

Annals of Gastroenterology and Digestive Disorders

Review Article

Open Access

Ki-67 Index and Somatostatin Receptor Expression as Prognostic Markers in Patients with Pancreatic Neuroendocrine Tumours: A Review

Isabel Moreno^{1*}, Anders Bergstrom² and Meera Krishnan³¹Department of Endocrine Oncology, University of Barcelona, Barcelona, Spain²Department of Nuclear Medicine, Uppsala University, Uppsala, Sweden³Department of Surgical Pathology, All India Institute of Medical Sciences, New Delhi, India

*Correspondence to: Isabel Moreno, Department of Endocrine Oncology, University of Barcelona, Barcelona, Spain

Received: 22 January 2025; Accepted: 9 April 2025; Published: 17 July 2025

Volume: 8; Issue: 1; ISSN: 2643-2609

Copyright: © 2025 IM, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

The Ki-67 proliferation index is the marker on which pancreatic neuroendocrine tumours are graded, and somatostatin receptor expression is the marker on which they are imaged and treated. They are usually discussed as a pair. In the one cohort that compared them directly, the receptor outperformed the proliferation index as a predictor of survival.

Objectives: To review the published evidence on Ki-67 and somatostatin receptor expression as prognostic markers in pancreatic neuroendocrine tumours: what each predicts, how reproducibly each is measured, how they relate to one another, and how immunohistochemistry compares with receptor imaging.

Material and Methods: Narrative review of resection cohorts, immunohistochemical series, imaging correlation studies and pooled analyses indexed in PubMed and the major oncology, pathology and nuclear medicine journals. Studies were eligible if they reported outcomes stratified by Ki-67 index or somatostatin receptor expression, the reproducibility of either measurement, or correlation between immunohistochemistry and receptor imaging. No new patient data were generated; every estimate quoted is one published by the original investigators.

Results: In 99 resected tumours, SSTR-2a was expressed in 80.1 per cent and SSTR-5 in 24.2 per cent. SSTR-2a positivity was associated with improved overall survival, with cumulative rates of 97.5, 91.5 and 82.9 per cent at one, three and five years, and on multivariable analysis it was the stronger predictor, with a hazard ratio of 0.2 (95% CI 0.1-0.8) against 0.8 (95% CI 0.1-5.7) for high Ki-67. SSTR-5 was not associated with survival. In a separate series of 279 patients, SSTR2 immunohistochemistry was an independent prognostic marker for overall survival (HR 0.82, 95% CI 0.67-0.99), correlated with tumour uptake on receptor imaging, but was outperformed by the imaging itself, which carried a positive predictive value advantage of 27 percentage points. Ki-67 measurement remains discrepant between observers precisely at the grade boundaries of 3 and 20 per cent.

Conclusion: Ki-67 is indispensable for grading but is measured least reliably at the thresholds that determine grade, and its prognostic weight in resected disease is smaller than the emphasis placed on it suggests. Somatostatin receptor status carries independent prognostic information and, where receptor imaging is available, the imaging is the more accurate of the two receptor measurements.

Abbreviations: PanNET – Pancreatic Neuroendocrine Tumour, PanNEN – Pancreatic Neuroendocrine Neoplasm, NEC – Neuroendocrine Carcinoma, SSTR – Somatostatin Receptor, IHC – Immunohistochemistry, DIA – Digital Image Analysis, WHO – World Health Organization, ENETS – European Neuroendocrine Tumour Society, PET – Positron Emission Tomography, PRRT – Peptide Receptor Radionuclide Therapy, SSA – Somatostatin Analogue, HR – Hazard Ratio, OS – Overall Survival, HPF – High-Power Field.

Keywords: Pancreatic Neuroendocrine Tumour; Ki-67; Somatostatin Receptor; Tumour Grading; Prognosis

Introduction

Pancreatic neuroendocrine neoplasms are uncommon, accounting for one to two per cent of pancreatic tumours, and their behaviour is notoriously difficult to predict from morphology alone [1]. Grading was placed on a proliferative footing when the European Neuroendocrine Tumour Society proposed cutoffs based on mitotic

rate and the Ki-67 index, a scheme subsequently adopted by the World Health Organization [1,2].

That system divides tumours at Ki-67 values of 3 and 20 per cent into grades 1, 2 and 3, with the highest grade later subdivided into well-differentiated grade 3 tumours and poorly differentiated carcinomas [2,3]. The grade drives surveillance intensity, eligibility for transplantation and the choice of systemic treatment [3].

Somatostatin receptors provide a second axis. Their overexpression is what makes these tumours visible on receptor-targeted positron emission tomography and treatable with somatostatin analogues and peptide receptor radionuclide therapy [4,5]. Receptor expression is therefore measured routinely, though usually as a predictive rather than a prognostic marker [6,7].

The two are commonly reported side by side, and the assumption is that Ki-67 carries the prognostic weight while the receptor determines treatment. The evidence reviewed here does not support that division cleanly. The aim is to set out what each marker predicts, how reliably each is measured, and what happens when they are compared directly in the same patients.

Material and Methods

Search strategy: PubMed and the archives of the major oncology, pathology and nuclear medicine journals were searched for studies of prognostic markers in pancreatic neuroendocrine tumours. Search terms combined pancreatic neuroendocrine tumour and neoplasm with Ki-67, proliferation index, WHO grading, somatostatin receptor, SSTR2, immunohistochemistry, DOTATATE, DOTANOC, interobserver variability and prognosis. Reference lists of retrieved studies were screened by hand.

Eligibility: Studies were included if they reported clinical outcomes stratified by Ki-67 index or somatostatin receptor expression in a defined population; the reproducibility of either measurement between observers or methods; or correlation between receptor immunohistochemistry and receptor imaging. Studies in neuroendocrine tumours of other primary sites are cited where they bear on the same measurement question and are identified as such.

Data extraction and handling: Design, sample size, antibody clone or tracer, scoring method, cutoff applied and reported effect estimates with confidence intervals were extracted as published. Cutoffs are reported alongside every result, because in this field the threshold chosen is frequently derived within the same cohort in which it is tested. No pooling or re-analysis was performed and no patient-level data were obtained. Figures 1 to 3 and Tables 1 and 2 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

What Ki-67 grading delivers: The proliferative grading system separates tumours that behave very differently. Survival in grade 3 disease is significantly worse than in grade 1 or grade 2, and within grade 3, poorly differentiated carcinomas fare significantly worse than well-differentiated grade 3 tumours [3]. Grade remains one of the two strongest predictors of outcome alongside stage [1]. Across pooled series, most resected tumours are grade 1 or grade 2, with grade 3 accounting for a small minority (Figure 3) [8].

The cutoffs themselves are contested. A Ki-67 threshold of 10 per cent is used to select candidates for transplantation and increasingly to select patients for somatostatin analogue or radionuclide therapy, and formal analysis of 190 resected tumours with a separate validation cohort of 145 identified 12 per cent as the discriminatory cutoff, close to that rule of thumb [9]. Other series have found better discrimination when grade 1 and grade 2 are separated at 5 per cent rather than 3 per cent [10]. The boundaries in current use were derived from limited numbers of cases and largely extrapolated from gastrointestinal rather than pancreatic tumours [9].

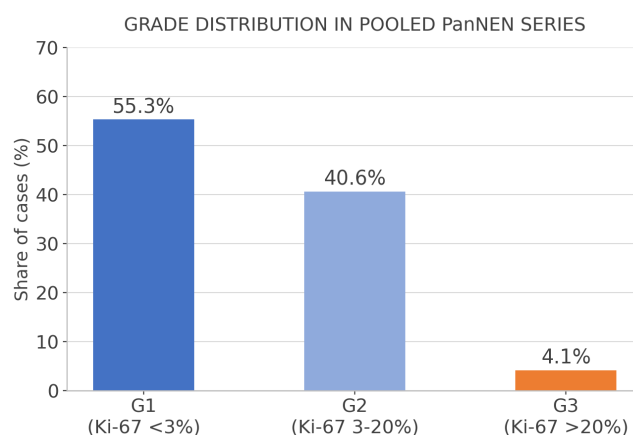


Figure 3: Distribution of WHO grade across pooled series of pancreatic neuroendocrine neoplasms [8]

The index is least reliable where it matters most: Ki-67 is a continuous measurement forced into categories, and the disagreement between observers concentrates at the category boundaries. A systematic review of digital image analysis in pancreatic neuroendocrine neoplasms found that even with manual counting from a printed image, the standardised method intended to reduce variability, discrepancies persisted specifically at the grade 1 to grade 2 transition at 3 per cent and the grade 2 to grade 3 transition at 20 per cent [8].

Digital analysis improved consistency in exactly those grey zones, but results still varied with hotspot selection and with the number of cells counted [8]. The eyeballing approach is discouraged in consensus documents yet remains widely used in daily practice [9]. In cytology cell blocks, grading concordance with the surgical specimen was 69 per cent by manual count and 55 per cent by digital analysis, and concordance was better for grade 1 than for grade 2 tumours [11].

Receptor expression carries independent prognostic weight: In a cohort of 99 resected pancreatic neuroendocrine tumours, SSTR-2a was expressed in 80 tumours (80.1 per cent) and SSTR-5 in 24 (24.2 per cent). SSTR-2a positivity was associated with improved overall survival on univariate analysis, with cumulative survival of 97.5, 91.5 and 82.9 per cent at one, three and five years (Figure 2). SSTR-5 expression showed no association with survival [12].

The multivariable result is the striking one. SSTR-2a positivity carried a hazard ratio of 0.2 (95% CI 0.1-0.8), while high Ki-67 carried a hazard ratio of 0.8 with a confidence interval spanning unity (95% CI 0.1-5.7) (Figure 1) [12]. In that cohort the receptor was the stronger prognostic indicator, and the proliferation index was not independently significant at all. Comparable associations between receptor expression and better outcome have been reported in well-differentiated endocrine carcinomas [13], in a series relating SSTR2A specifically to outcomes in pancreatic tumours [14], and across gastroenteropancreatic sites more broadly [15,16,17]. The same relationship holds outside the pancreas: in 350 resected rectal neuroendocrine tumours, SSTR2 expression was associated with smaller tumours, lower stage and better outcome [22].

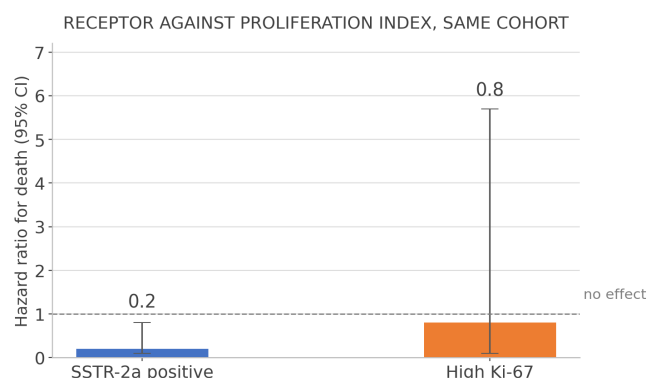


Figure 1: Multivariable hazard ratios for overall survival in 99 resected tumours, receptor status against proliferation index [12]

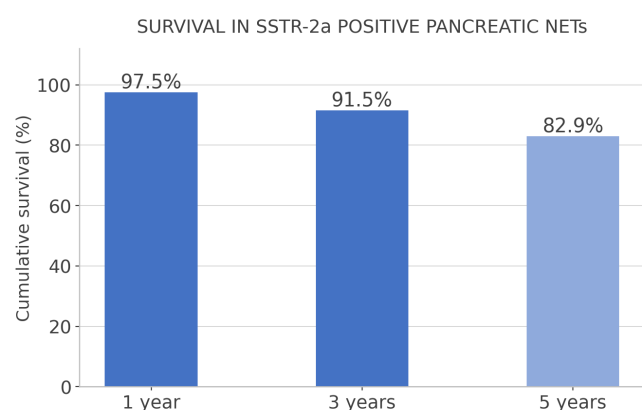


Figure 2: Cumulative overall survival in SSTR-2a-positive pancreatic neuroendocrine tumours [12]

Study	n	Marker	Principal reported finding
Corleto et al. 2009 [13]	—	SSTR2, SSTR5	Both associated with better survival
Okuwaki et al. 2013 [14]	—	SSTR2A	Receptor expression related to outcome in PanNETs
Mehta et al. 2015 [12]	99	SSTR-2a, Ki-67	SSTR-2a HR 0.2 against Ki-67 HR 0.8
Song et al. 2016 [16]	—	SSTR subtypes	Subtype-specific prognostic value in PanNETs
Brunner et al. 2017 [18]	279	SSTR2 IHC and imaging	Imaging more accurate than immunohistochemistry
Ki-67 pooled review [8]	—	Ki-67	Discrepancies persist at the 3% and 20% boundaries

Table 1: Principal studies reviewed, with the marker examined and the finding as reported by the original investigators

Imaging beats the stain: The largest comparison assembled a tissue microarray and imaging database from 279 patients with neuroendocrine tumours, some treated with receptor-targeted radiopeptide therapy. SSTR2 immunohistochemistry was an independent prognostic marker for overall survival, with a hazard ratio of 0.82 (95% CI 0.67-0.99, $p = 0.037$). Among patients treated with radiopeptide therapy, receptor expression on immunohistochemistry correlated with tumour uptake on imaging ($n = 170$, $p < 0.001$) [18].

But the imaging was the better prognostic test. Receptor-targeted imaging showed a positive predictive value advantage of 27 percentage points (95% CI 3-56, $p = 0.025$) over the stain [18]. That is a coherent result rather than a paradox: a biopsy stains one fragment of one lesion, while imaging reports receptor status across

every deposit in the body, and in a disease where lesions differ from one another that whole-body view is worth more.

Prospective correlation supports the same picture. In a series of non-functional pancreatic neuroendocrine neoplasms assessed by dual-tracer imaging with receptor and glucose analogues alongside staining for all five receptor subtypes, SSTR2 was the only subtype that correlated with receptor tracer uptake, and high SSTR5 expression correlated with a low Ki-67 index [19]. Earlier work comparing scintigraphy with immunohistochemistry reached compatible conclusions [20,21].

Measurement	What it reports	Principal limitation
Ki-67 by manual count	Proliferative fraction in a selected hotspot	Discrepant at the 3% and 20% grade boundaries [8,9]
Ki-67 by digital analysis	The same, more reproducibly	Varies with hotspot choice and cell count [8,11]
SSTR2 immunohistochemistry	Receptor status in one sampled fragment	Independent prognostic value but bettered by imaging [12,18]
Receptor-targeted imaging	Receptor status across all lesions	Requires tracer access; not universally available [18,19]

Table 2: The four measurements in routine use, what each reports and the limitation described for it

Discussion

Two conclusions follow, and the first is uncomfortable for the way these tumours are reported. Ki-67 is the basis of grading and grading drives management, yet the index is measured least reliably at exactly the values that decide the grade [8]. A tumour reported at 3 per cent and one reported at 2 per cent may differ only in who counted, and they will be managed differently. Digital analysis narrows the gap without closing it [8,11].

The second is that receptor status is not merely predictive. In the one cohort that tested both in the same multivariable model, SSTR-2a was independently prognostic and Ki-67 was not [12], and a much larger series confirmed independent prognostic value for SSTR2 [18]. The habit of treating the receptor as a treatment-selection marker and the proliferation index as the prognostic one is not well supported.

Two measurements of the same thing

The comparison between receptor staining and receptor imaging deserves emphasis because it generalises. Both measure the same biology, but one samples a fragment and the other surveys the whole patient, and the whole-body measurement was the more accurate predictor by a wide margin [18]. Where receptor imaging has been performed, the histological receptor score adds little prognostic information beyond it.

A practical corollary concerns which sample is graded. Cytology cell blocks agree with the resection specimen in only around two-thirds of cases, and worse for grade 2 tumours [11], so a grade assigned on fine-needle material should be treated as provisional where it sits near a threshold.

Study limitations

The limitations belong to the underlying literature. The head-to-head comparison of receptor and proliferation index rests on 99 patients from a single institution, and the wide confidence interval around the Ki-67 hazard ratio reflects that the study was not powered to exclude an effect [12]. Cutoffs for both markers are frequently derived and tested within the same cohort, which inflates apparent discrimination [9,10]. Antibody clones, scoring systems and H-score thresholds differ between series, so receptor positivity rates are not directly

comparable [12,17]. Several informative series include neuroendocrine tumours of mixed primary site, and receptor expression differs by site of origin [15,17]. The imaging comparison was conducted in a population enriched for patients selected for radiolabeled peptide therapy, which may not represent unselected practice [18].

Two gaps deserve naming. No prospective study has compared management guided by receptor status against management guided by grade, so the relative prognostic weight established in retrospective cohorts has not been translated into a decision rule. And no study reviewed here reports outcomes for patients whose grade changed on re-review, which is the population most affected by the measurement variability described [8,11].

Conclusion

Ki-67 remains the basis of grading in pancreatic neuroendocrine tumours and grading remains one of the two strongest predictors of outcome. But the index is measured with least agreement at the 3 and 20 per cent boundaries that determine grade, its cutoffs were derived from limited data and partly extrapolated from other sites, and in the one cohort that tested both markers together it was the weaker predictor. Somatostatin receptor expression, usually treated as a treatment-selection marker, carries independent prognostic information, and where receptor imaging is available it predicts survival more accurately than the corresponding stain because it surveys every lesion rather than one fragment. Reporting both, and treating a grade assigned near a threshold or on cytology material as provisional, is what the published evidence supports.

Acknowledgements

The surgical series, tissue microarray projects and imaging registries on which this article draws were assembled by others, and the credit is theirs.

Funding

No grant, contract or institutional subsidy of any kind was received towards the preparation of this article.

Conflict of Interest

There is no competing interest to declare on the part of any author.

Ethics Statement

This is a review of material that has already appeared in print. Since no one was enrolled and no fresh clinical records were opened, the question of ethical approval did not arise.

References

1. Basturk O, Yang Z, Tang LH, Hruban RH, Adsay V, et al. "The high-grade (WHO G3) pancreatic neuroendocrine tumor category is morphologically and biologically heterogeneous and includes both well differentiated and poorly differentiated neoplasms". *Am J Surg Pathol* 39(2015):683-690.
2. Rindi G, Klöppel G, Albarello L, Alexiev V, Anlauf M, et al. "TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system". *Virchows Arch* 449(2006):395-401.
3. Yang M, Zeng L, Zhang Y, Wang WG, Wang L, et al. "World Health Organization grading classification for pancreatic neuroendocrine neoplasms: a comprehensive analysis from a large Chinese institution". *BMC Cancer* 20(2020):906.
4. Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, et al. "Phase 3 trial of 177Lu-Dotatate for midgut neuroendocrine tumors". *N Engl J Med* 376(2017):125-135.
5. Caplin ME, Pavel M, Wink DA, Phan AT, Raderer M, et al. "Lanreotide in metastatic enteropancreatic neuroendocrine tumors". *N Engl J Med* 371(2014):224-233.
6. Rinke A, Müller HH, Schade-Brittinger C, Klose KJ, Barth P, et al. "Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors (PROMID)". *J Clin Oncol* 27(2009):4656-4663.
7. Bodei L, Mueller-Brand J, Baum RP, Pavel ME, Horsch D, et al. "The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRT) in neuroendocrine tumours". *Eur J Nucl Med Mol Imaging* 40(2013):800-816.
8. Owens R, Gilmore E, Bingham V, Cardwell C, McBride H, et al. "Ki-67 assessment of pancreatic neuroendocrine neoplasms: systematic review and meta-analysis of manual vs. digital pathology scoring". *Mod Pathol* 35(2022):712-720.
9. Xue Y, Reid MD, Pehlivanoglu B, Obeng RC, Jiang H, et al. "Subgrading of G2 pancreatic neuroendocrine tumors as 2A (Ki67 3% to <10%) versus 2B (10% to ≤20%) identifies behaviorally distinct subsets in keeping with the evolving management protocols". *Ann Surg Oncol* 29(2022):6773-6784.
10. Genc CG, Jilesen AP, Partelli S, Falconi M, Muffatti F, et al. "Recurrence of pancreatic neuroendocrine tumors and survival predicted by Ki67". *Ann Surg Oncol* 25(2018):2467-2474.
11. Weiss VL, Kiernan C, Wright J, Merchant NB, Coogan AC, et al. "Fine-needle aspiration-based grading of pancreatic neuroendocrine neoplasms using Ki-67: is accurate WHO grading possible on cytologic material?". *J Am Soc Cytopathol* 7(2018):154-459.
12. Mehta S, de Reuver PR, Gill P, Andrici J, D'Urso L, Mittal A, Pavlakakis N, Clarke S, Samra JS, Gill AJ. "Somatostatin receptor SSTR-2a expression is a stronger predictor for survival than Ki-67 in pancreatic neuroendocrine tumors". *Medicine (Baltimore)* 94(2015):e1281.
13. Corleto VD, Falconi M, Panzuto F, Milione M, De Luca O, Perri P, Cannizzaro R, Bordi C, Pederzoli P, Scarpa A, Delle Fave G. "Somatostatin receptor subtypes 2 and 5 are associated with better survival in well-differentiated endocrine carcinomas". *Neuroendocrinology* 89(2009):223-230.
14. Okuwaki K, Kida M, Mikami T, Yamauchi H, Imaizumi H, Miyazawa S, Iwai T, Takezawa M, Saegusa M, Watanabe M, Koizumi W. "Clinicopathologic characteristics of pancreatic neuroendocrine tumors and relation of somatostatin receptor type 2A to outcomes". *Cancer* 119(2013):4094-4102.
15. Qian ZR, Li T, Ter-Minassian M, Yang J, Chan JA, et al. "Association between somatostatin receptor expression and clinical outcomes in neuroendocrine tumors". *Pancreas* 45(2016):1386-1393.
16. Song KB, Kim SC, Kim JH, Seo DW, Hong SM, et al. "Prognostic value of somatostatin receptor subtypes in pancreatic neuroendocrine tumors". *Pancreas* 45(2016):187-192.
17. Wada H, Matsuda K, Akazawa Y, Yamaguchi Y, Miura S, et al. "Expression of somatostatin receptor type 2A and PTEN in neuroendocrine neoplasms is associated with tumor grade but not with site of origin". *Endocr Pathol* 27(2016):179-187.
18. Brunner P, Jörg AC, Glatz K, Bubendorf L, Radojewski P, et al. "The prognostic and predictive value of sstr2-immunohistochemistry and sstr2-targeted imaging in neuroendocrine tumors". *Eur J Nucl Med Mol Imaging* 44(2017):468-475.
19. Majala S, Vesterinen T, Seppanen H, Mustonen H, Sundstrom J, et al. "Correlation of somatostatin receptor 1-5 expression, [68Ga]Ga-DOTANOC, [18F]F-FDG PET/CT and clinical outcome in a prospective cohort of pancreatic neuroendocrine neoplasms". *Cancers* 14(2022):162.
20. Sclafani F, Carnaghi C, Di Tommaso L, Rodari M, Destro A, Rimassa L, Giordano L, Chiti A, Roncalli M, Santoro A. "Detection of somatostatin receptor subtypes 2 and 5 by somatostatin receptor

- scintigraphy and immunohistochemistry: clinical implications in the diagnostic and therapeutic management of gastroenteropancreatic neuroendocrine tumors". *Tumori* 97(2011):620-628.
21. Diakatou E, Alexandraki KI, Tsolakis AV, Kontogeorgos G, Chatzellis E, Leonti A, Kaltsas GA. "Somatostatin and dopamine receptor expression in neuroendocrine neoplasms: correlation of immunohistochemical findings with somatostatin receptor scintigraphy visual scores". *Clin Endocrinol* 83(2015):420-428.
22. Kim JY, Kim J, Kim YI, Yang DH, Yoo C, Park IJ, Ryoo BY, Ryu JS, Hong SM. "Somatostatin receptor 2 (SSTR2) expression is associated with better clinical outcome and prognosis in rectal neuroendocrine tumors". *Sci Rep* 14(2024):4047.

Citation: Moreno I, Bergstrom A, Krishnan M. "Ki-67 Index and Somatostatin Receptor Expression as Prognostic Markers in Patients with Pancreatic Neuroendocrine Tumours: A Review." *Ann Gastroenterol Dig Disord* (2025) Volume 8, Issue 1 doi: 10.5281/zenodo.22202865