Compassionate AI in Clinical Care: Feasibility Assessment of a Rules-Based Algorithm to Support a Nurse-Led Model of Care for Prostate Cancer Survivorship

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Abstract

To support patients in managing the chronic symptoms associated with prostate cancer (PCa) survivorship, the expert system *Ned* algorithm is intended to support the introduction of a nurse-led model of care. It builds upon the existing *Ned* application that facilitates virtual follow-up visits between patients and their care team. This study aims to assess the feasibility of the *Ned* algorithm to support a high patient to nurse ratio in a clinical setting for streamlined supportive care. The simulations presented here were conducted on a retrospective dataset to characterize the algorithm's outputs. Results demonstrate feasibility to support self-management of symptoms in over 80% of cases. This provides evidence that the algorithm will effectively support nurses in triaging PCa survivors between routine follow-up visits, while encouraging patients to successfully self-manage their symptoms.

1 Introduction

Prostate cancer (PCa) survivorship is associated with chronic symptoms which are traditionally managed through in-person follow-up visits between patients and physicians. With increasing frequency of PCa occurrence and high rates of survival, significant clinical resources must be dedicated to survivorship care [1-3]. Ned is an application developed by the Centre for Digital Therapeutics at the University Health Network, which aims to facilitate virtual visits between patients and their care team. Recent research has demonstrated improved clinical efficiency and patient satisfaction with nurse-led models of care [4, 5]. Building upon this, the next iteration of Ned will introduce a nurse-led model of care, mediated by an algorithm. The Ned algorithm will (1) provide decision support to nurses based on patient-reported outcomes informed by their symptoms, and (2) provide patients with tailored actionable, prescriptive and educational resources to encourage patient empowerment and self-management of symptoms.

One popular patient-reported outcomes survey is the Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP). EPIC-CP is a clinically validated questionnaire designed to assess health-related quality of life among PCa patients [6]. Questions associated with related symptoms are classified within one of five domains: urinary incontinence (UI), urinary irritation/obstruction (UIO), bowel function (BF), sexual function (SF), and hormonal function (HF) [6]. The *Ned* algorithm will assess patients based on their EPIC-CP responses, collected through the *Ned* application on a monthly basis. The patient's status is escalated if:

- 1. Pre-defined domain delta thresholds are exceeded. These deltas compute the change in domain scores relative to the previous month (local delta) and the patient's baseline (baseline delta).
- Key clinically urgent questions (CUQ) thesholds are exceeded. These CUQ address pain or burning with urination, weak urine stream/incomplete emptying, hematuria, bloody stools, and depression. CUQs are associated with symptoms that require further clinical assessment and were identified in consultation with clinical experts and Cancer Care Ontario guidelines [7–12].
- 3. Individual patient history of alerting.

The algorithm supports compassionate care by honouring patient preference. While the default is to provide patients with resources to self-manage their symptoms, for higher alert states, patients are asked if they would prefer a virtual visit with the *Ned* nurse. Four alert states are output by the algorithm:

- · Green: Normal results; no intervention is required.
- Yellow: Patient's first abnormal domain score; tailored, prescriptive education resources are provided.
- Orange: Clinically urgent symptoms present OR history of abnormal domain scores; tailored, prescriptive education re-

sources are provided and the option to meet virtually with the *Ned* nurse is extended.

• Red: Generated when the patient accepts the option to meet with the *Ned* nurse.

The *Ned* algorithm will provide streamlined decision support for nurses to support a high patient to nurse ratio. This will facilitate improved clinical efficiency with a nurse-led model of care and is positioned to provide higher quality compared to traditional PCa followup. By providing patients with tailored, actionable, prescriptive self-management resources, the *Ned* algorithm will empower patients in their self-care and introduce compassionate artificial intelligence (AI) in a clinical setting.

In effort to promote trust, transparency, and pragmatic acceptability to support the clinical application of the *Ned* algorithm, its rules have been defined in collaboration with clinicians and consultation of Cancer Care Ontario guidelines [7–12]. While machine learning (ML) approaches could have been employed to define and optimize escalation thresholds, algorithm interpretability is a critical element for clinical translation of AI [13–15]. This supports an expert rules-based approach to algorithm design. Specifically, rules and recommendations must be fully understood and interpretable by nurses for intuitive triaged alert response. Additionally, significant amounts of data are required to develop robust and reliable ML algorithms. Given the limited availability of longitudinal EPIC-CP data, a rules-based approach informed by clinical experts was determined to be most appropriate to facilitate clinical acceptability.

The purpose of this analysis is to assess the pragmatic feasibility of the Ned algorithm and to characterize the alerts generated, prior to its clinical deployment. Additionally, this study aims to: (1) identify the appropriate thresholds to support clinical feasibility (i.e., high patient to nurse ratio), and (2) maintain a transparent methodology to foster trust in this AI-powered algorithm and the decision support it provides. The Ned algorithm is expected to be feasible for clinical implementation if at least 80% of alerts generated can be self-resolved. Based on a similar established nurse-led model of care, developed by our group at the University Health Network for heart failure, one Medly nurse can care for several hundred patients daily. We have found this to be possible using our data usage statistics because 80% of alerts are patient-resolved with patientfacing actionable feedback. While resolution timing urgency differs between heart failure and PCa, we anticipate a similarly high nurse to patient ratio being feasible. As such, our preliminary validation uses the same target of 80% of alerts being self-resolved by patients.

2 Methods

The process of developing the *Ned* algorithm and pilot data collection was reviewed by the University Health Network (UHN) Research Ethics Board as part of a quality improvement initiative (REB QID: 20-0114).

We evaluated algorithm outputs to characterize the ratio of alerts generated by running simulations of the algorithm at different thresholds using *Ned* pilot data from 21 patients with Expanded Prostate Cancer Index Composite-26 (EPIC-26) scores at a single time point. To evaluate longitudinal changes in patient scores, the pilot data was supplemented with the median EPIC-26 scores reported by Einstein *et al.*, which were used as the baseline response for all pilot study responses [16]. All EPIC-26 scores were converted to EPIC-CP equivalents with guidance from a clinical expert.

We calculated the algorithm's simulated output using the Einstein *et al.* medians [16] as our simulated baseline, and *Ned* pilot data as the present time point (i.e., time point 1). Since patient preference was not part of this retrospective data, possible alert state outputs were: orange, yellow, and green. Here, orange alert states could require clinical intervention by the *Ned* nurse, with yellow and green alerts self-managed by the patient. Table 1 summarizes the threshold values for each simulation's domain and clinically urgent questions along with the expected impact of the modified thresholds on the algorithm's sensitivity.

Table 1: Summary of Simulation TI	hresholds and	Expected	Impact
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Simulation	EPIC-26 Item	Threshold	Expected Impact on Sensitivity
1	UI UIO BF SF HF CUQ	0 1 1 1 0 0	Pre-defined,clinically-informed thresholds used as baseline comparison.
2	UI UIO BF SF HF CUQ	0 1 1 1 0 1	Decrease sensitivity to CUQ by one point.
3	UI UIO BF SF HF CUQ	1 2 2 2 1 0	Decrease domain sensitivity one point.
4	UI UIO BF SF HF CUQ	1 1 3 5 2 1	Decrease domain sensitivity by capturing deltas greater than sum of mean and standard deviation. Decrease sensitivity to CUQ by one point.
5	UI UIO BF SF HF CUO	1 1 3 5 2 2	Decrease domain sensitivity by capturing deltas greater than sum of mean and standard deviation. Decrease sensitivity to CUQ by two points.

UI = Urinary Incontinence; UIO = Urinary Irritation/Obstruction; BF = Bowel Function; SF = Sexual Function; HF = Hormonal Function; CUQ = Clinically Urgent Questions

The algorithm alert output provides data-driven feedback to inform the nurse when clinical intervention is warranted (or additionally at their discretion). Therefore, the proportions of alerts generated at time point 1 were used to assess the feasibility of clinical deployment of the algorithm. Since eligibility criteria for *Ned* enrollment requires that patients are stable with low risk of PCa recurrence, managing the algorithm in a clinical setting is expected to be feasible if at least 80% of alerts generated can be managed independently by the patient [17]. To provide a conservative estimate, we assumed that all orange alerts could require clinical intervention. In reality, this is an overestimate depending on patient preference for a visit with the *Ned* nurse. Regarding feasibility assessment, only alerts computed from *Ned* pilot data at time point 1 were considered based on the proportions of alerts generated.

We summarized the simulated *Ned* algorithm results using descriptive statistics. Abnormal domain scores were identified when the local and baseline deltas exceed their associated threshold, therefore, the mean, standard deviation, and range of the deltas for each domain between baseline and time point 1 were used to understand the patterns of generated alerts. Based on the defined feasibility criteria, most deltas (i.e., approximately 80%) should be lower than the defined domain threshold. Therefore, an optimal threshold could be above the sum of the mean and standard deviation, while the range should capture abnormal scores that exceed the threshold.

The mode alerting domain was used to assess the relevance of the thresholds and resources provided for each domain based on the domains most frequently associated with needing follow-up care. This statistic will inform whether more targeted resources are required for specific domains in the future.

3 Results

Table 2 summarizes the proportion of alert states output by the algorithm in each simulation and the associated mode alerting domains using the median EPIC-26 scores reported by Einstein *et al.* as baseline data and *Ned* pilot data as time point 1. The mode alerting domains highlight the domain that was most frequently associated with triggering yellow or orange output alert states.

Thresholds used in simulations 1 and 3 yielded proportional alerts that do not support clinical feasibility with the proportion of orange alerts exceeding the target of 20%. Thresholds used in simulations 2 and 4 provide a proportion of orange alerts slightly

Table 2: Proportional Alert Generation across Simulations

Simulation	Orange	Yellow	Green	Mode Alerting
	Alerts	Alerts	Alerts	Domains
1	57%	24%	19%	UIO
2	24%	57%	19%	SF
3	57%	24%	19%	UIO
4	24%	24%	52%	UIO
5	14%	29%	57%	UI, UIO, SF

exceeding the target of 20% at 24% orange alerts and with only one mode alerting domain in each simulation (S2: sexual function; S4: urinary irritation/obstruction). Thresholds used in simulation 5 achieve the target of 20% or less of orange alerts generated (14%) with trimodal alerting domains for urinary incontinence, urinary irritation/obstruction, and sexual function domains.

4 Discussion

The Ned algorithm was designed to support a nurse-led model of care for PCa survivorship by generating alerts which serve as decision aids by informing the Ned nurse of patients most in need of follow-up care. Clinical management of these alerts is expected to be feasible if at least 80% of alerts generated can be independently resolved by the patient using the self-management resources output by the algorithm. The target of at least 80% of alerts supporting independent resolution without clinical intervention was achieved in simulation 5, while simulations 2 and 4 approached this target, with orange alerts constituting only 24% of the total alerts generated. Orange alerts provide patients with the option to visit with the *Ned* nurse, therefore, the total number of orange alerts is likely an overestimate of the number of alerts requiring clinical intervention, indicating that the thresholds used in simulations 2 and 4 are plausible options while maintaining a higher sensitivity than simulation 5. However, simulation 5 resulted in the highest proportion of green alerts. Although there was limited time-series data in this analysis, to support clinical feasibility, minimizing the proportion of yellow alerts may be preferred by patients navigating their symptom chronicity. Since orange alerts can also be triggered from abnormal domain scores if patients have previously had abnormal scores on the same domain, a higher proportion of yellow alerts is likely to be associated with an increased proportion of orange alerts over time. In practice, the converse trend may be preferred but warrants corroboration from clinical staff and patient perspectives. Regardless, the results of this analysis provide supportive evidence for a plausibly high patient to nurse ratio to have meaningful clinical impacts through the introduction of the Ned algorithm by implementing the thresholds used in simulation 5.

Adoption of the modified thresholds will require continued discussion and endorsement by clinical collaborators to inform and evaluate the impact to the clinical workflow. An important consideration in defining alert thresholds is the trade-off between sufficient threshold sensitivity to ensure that alerts are escalated according to patient needs, while avoiding inappropriately high alert frequencies which contribute to alert fatigue. Regarding potential safety considerations, as the *Ned* algorithm is intended to aid in managing treatment side effect chronicity, patients continue to be monitored for PCa recurrence through traditional follow-up visits with their medical team. This means that reducing the sensitivity of thresholds will not cause serious harm to patients.

Next steps to validate these findings include increasing the scope of analysis using a larger dataset including time series data. The small sample size and limited scope of the dataset studied is a limitation of this analysis. Analyzing data from a larger sample of patients will reduce sample bias while improving the reliability, validity, and generalizability of the results. Additionally, median EPIC-26 scores reported in literature were assumed to represent the baseline scores for all patients in this study. Although this data represents the EPIC-26 scores of PCa patients in general, it may not reflect the natural individual variability in baseline scores of the patient sample studied. By analyzing a longitudinal dataset with EPIC-26 scores linked to patients between time points, this limitation will be addressed while permitting further assessment of the impact of both local and baseline deltas and escalation based on previous alerts. Since PCa survivorship is associated with long-term, chronic symptoms, a study of longitudinal data will also enhance the feasibility

assessment of the algorithm over a longer duration of time, in align- Acknowledgments ment with its intended clinical use.

Moving forward, the Ned algorithm will include one additional question and since this is unique to the Ned algorithm, it is not collected through the EPIC-26 and could not be accounted for in this analysis. The implication of adding one question is the potential to increase the proportion of yellow and orange alerts. The Ned algorithm will additionally account for patient preference, which cannot be assessed in this analysis. Therefore the alert proportions for orange alerts are likely overestimates of what would become red alerts and warrant direct nurse interaction. Here, we assumed that all orange alerts will require nurse interaction. Implementing patient preference as the deciding factor differentiating orange from red alerts will decrease the number of nurse interactions required. This implies that the results of simulation 5 with >80% alerts selfresolved, will be even better platformed to feasibly support a high patient to nurse ratio.

To address the subjectivity of symptom severity associated with the chronic nature of PCa, in the future, additional consideration should be given to the implementation of personalized thresholds. The current analysis focused on characterizing the alerts generated when the same thresholds were applied for all patients. However, to support self-management of symptoms and promote patient autonomy, it would be valuable to explore the impact of using different thresholds to address the individual needs of each patient. One approach to achieve this is to determine the appropriate sensitivity of thresholds based on EPIC-CP questions that prompt patients to assess how big of a problem key symptoms are. Since these questions assess the patients' perception of their symptoms, they provide a patient-directed means to assess the degree of intervention that would provide meaningful assistance to the patient.

Alternatively, ML approaches could be employed to learn the optimal thresholds for classification based on EPIC-CP scores. Conditional upon the availability of suitable training data, ML approaches provide the potential for optimized thresholds to be learned. Likewise, ML could be employed to deliver more personalized care by identifying the optimal personalized thresholds for each patient and accounting for their baseline scores and perception of symptom severity.

While the EPIC-CP is a valuable tool for assessment of patientreported symptoms, clinical evaluation of PCa patients and survivors involves assessment of several additional clinical indicators, including prostate-specific antigen (PSA) levels. Building upon the current algorithm to include several clinical indicators will further support data-driven evaluation of patient needs enhancing the delivery of self-management resources. Especially in this case, there exists an advantageous opportunity for ML to enhance clinical decision support. Currently, there is a lack of consensus in literature regarding the PSA thresholds that are clinically significant [18-22]. Provided transparency and interpretability to facilitate trust and clincal uptake, ML may therefore be uniquely positioned to account for multiple clinical indicators, including PSA through learned and optimised alert escalation thresholds identified that model the complex relationships between EPIC-CP scores and other clinical features.

Conclusion 5

With the current landscape and limited available datasets, a rules based approach was deemed most appropriate to promote trust and transparency in the clinical implementation of the Ned algorithm. Simulations of the Ned algorithm provide supportive evidence for alerts managed through a high patient to nurse ratio. Specifically, implementing the thresholds used in simulation 5 achieves the desired proportion of alerts with over 80% self-resolved. While supporting patient preference and autonomy, this exploratory validation study suggests compassionate AI can feasibly support a nurse-led model of empowered PCa patient self-management. Future directions include further validation of results to address limitations of the current analysis, as well as building upon the current algorithm to expand its predictive capacity and accuracy. Use of ML methods should also be considered as they are well suited to learn optimal thresholds for alert escalation while accounting for additional clinical indicators and patient perception of symptom severity.

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References

- [1] J. Dunn, A. Green, N. Ralph, R. U. Newton, A. Kneebone, M. Frydenberg, and S. K. Chambers, "Prostate cancer survivorship essentials framework: guidelines for practitioners," BJU International, vol. 128, pp. 18-29, Aug. 2020. [Online]. Available: https://bjui-journals-onlinelibrary-wiley-com.proxy. lib.uwaterloo.ca/doi/10.1111/bju.15159
- [2] F. Bray, J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A. Torre, and A. Jemal, "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries," CA: A Cancer Journal for Clinicians, vol. 68, no. 6, pp. 394-424, 2018. [Online]. Available: https://onlinelibrary.wiley.com/doi/abs/10.3322/caac.21492
- [3] Y. Fradet, L. Klotz, J. Trachtenberg, and A. Zlotta, "The burden of prostate cancer in Canada," Canadian Urological Association Journal, vol. 3, no. 3 Suppl 2, pp. S92–S100, Jun. 2009. [Online]. Available: https: //www.ncbi.nlm.nih.gov/pmc/articles/PMC2698782/
- [4] M. Oatley and M. Fry, "A nurse practitioner-led model of care improves access, early assessment and integration of oncology services: an evaluation study," Supportive Care in Cancer, vol. 28, no. 10, pp. 5023-5029, Oct. 2020. [Online]. Available: https://doi.org/10.1007/s00520-019-05292-0
- [5] M. Jefford, S. Aranda, K. Gough, K. Lotfi-Jam, P. Butow, M. Krishnasamy, J. Young, J. Phipps-Nelson, L. Russell, D. King, and P. Schofield, "Evaluating a nurse-led survivorship care package (SurvivorCare) for bowel cancer survivors: study protocol for a randomized controlled trial," Trials, vol. 14, no. 1, p. 260, Aug. 2013. [Online]. Available: https://doi.org/10.1186/1745-6215-14-260
- [6] T. A. Skolarus, R. L. Dunn, M. G. Sanda, P. Chang, T. K. Greenfield, M. S. Litwin, J. T. Wei, M. Regan, L. Hembroff, J. T. Wei, D. Hamstra, R. Dunn, L. Northouse, D. Wood, E. A. Klein, J. Ciezki, J. Michalski, G. Andriole, M. Litwin, C. Saigal, T. Greenfield, L. Pisters, D. Kuban, H. Sandler, J. Hu, A. Kibel, D. Dahl, A. Zietman, Chang, A. Wagner, I. Kaplan, and M. G. Sanda, "Minimally Important Difference for the Expanded Prostate Cancer Index Composite Short Form," Urology, vol. 85, no. 1, pp. 101-106, Jan. 2015. [Online]. Available: https: //linkinghub.elsevier.com/retrieve/pii/S0090429514009893
- Ontario, "Expanded Prostate [7] Cancer Care Cancer Index Composite for Clinical Practice (EPIC-CP) Prostate Cancer Quality of Life (QOL)." [Online]. Available: https://www.cancercareontario.ca/sites/ccocancercare/ files/assets/CCOEPIC-English.pdf
- [8] Cancer Care Ontario, "Urinary Incontinence Prostate Cancer." [Online]. Available: https://www.cancercareontario. ca/en/symptom-management/35056
- [9] Cancer Care Ontario, "Urinary Problems Prostate Cancer." [Online]. Available: https://www.cancercareontario.ca/en/ symptom-management/35061
- [10] Cancer Care Ontario, "Bowel Function Prostate Can-cer." [Online]. Available: https://www.cancercareontario.ca/en/ symptom-management/35041
- [On-Care "Sexual [11] Cancer Ontario, Health." line]. Available: https://www.cancercareontario.ca/en/ symptom-management/35051
- [12] Cancer Care Ontario, "Hormonal Symptoms Prostate Cancer." [Online]. Available: https://www.cancercareontario. ca/en/symptom-management/35046

- [13] S. Wongvibulsin, K. C. Wu, and S. L. Zeger, "Improving Clinical Translation of Machine Learning Approaches Through Clinician-Tailored Visual Displays of Black Box Algorithms: Development and Validation," *JMIR Medical Informatics*, vol. 8, no. 6, p. e15791, Jun. 2020. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7312245/
- [14] E. H. Shortliffe and M. J. Sepúlveda, "Clinical Decision Support in the Era of Artificial Intelligence," *JAMA*, vol. 320, no. 21, pp. 2199–2200, Dec. 2018. [Online]. Available: https://doi.org/10.1001/jama.2018.17163
- [15] T. M. Maddox, J. S. Rumsfeld, and P. R. O. Payne, "Questions for Artificial Intelligence in Health Care," *JAMA*, vol. 321, no. 1, pp. 31–32, Jan. 2019. [Online]. Available: https://doi.org/10.1001/jama.2018.18932
- [16] D. J. Einstein, D. Patil, J. Chipman, M. M. Regan, K. Davis, C. M. Crociani, A. A. Wagner, M. G. Sanda, and P. Chang, "Expanded Prostate Cancer Index Composite-26 (EPIC-26) Online: Validation of an Internet-Based Instrument for Assessment of Health-Related Quality of Life After Treatment for Localized Prostate Cancer," *Urology*, vol. 127, pp. 53–60, May 2019. [Online]. Available: https://www.sciencedirect.com/ science/article/pii/S0090429519301529
- [17] Q. Pham, J. Hearn, J. L. Bender, A. Berlin, I. Brown, D. Bryant-Lukosius, A. H. Feifer, A. Finelli, G. Gotto, R. Hamilton, R. Rendon, and J. A. Cafazzo, "Virtual care for prostate cancer survivorship: protocol for an evaluation of a nurse-led algorithm-enhanced virtual clinic implemented at five cancer centres across canada," *BMJ Open*, vol. 11, no. 4, 2021. [Online]. Available: https: //bmjopen.bmj.com/content/11/4/e045806
- [18] T. Van den Broeck, R. C. N. van den Bergh, E. Briers, P. Cornford, M. Cumberbatch, D. Tilki, M. De Santis, S. Fanti, N. Fossati, S. Gillessen, J. P. Grummet, A. M. Henry, M. Lardas, M. Liew, M. Mason, L. Moris, I. G. Schoots, T. van der Kwast, H. van der Poel, T. Wiegel, P.-P. M. Willemse, O. Rouvière, T. B. Lam, and N. Mottet, "Biochemical Recurrence in Prostate Cancer: The European Association of Urology Prostate Cancer Guidelines Panel Recommendations," *European Urology Focus*, vol. 6, no. 2, pp. 231–234, Mar. 2020. [Online]. Available: https://www. sciencedirect.com/science/article/pii/S2405456919301592
- [19] M. Roach, G. Hanks, H. Thames, P. Schellhammer, W. U. Shipley, G. H. Sokol, and H. Sandler, "Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: Recommendations of the RTOG-ASTRO Phoenix Consensus Conference," *International Journal of Radiation Oncology*Biology*Physics*, vol. 65, no. 4, pp. 965–974, Jul. 2006. [Online]. Available: https://www.sciencedirect.com/ science/article/pii/S0360301606006638
- [20] L. Klotz, B. Shayegan, C. Guillemette, L. L. Collins, G. Gotto, D. Guérette, M.-P. Jammal, T. Pickles, P. O. Richard, and F. Saad, "Testosterone suppression in the treatment of recurrent or metastatic prostate cancer — A Canadian consensus statement," *Canadian Urological Association Journal*, vol. 12, no. 2, pp. 30–37, Feb. 2018. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/ PMC5937399/
- [21] R. Gilbert, K. Tilling, R. M. Martin, J. A. Lane, M. Davis, F. C. Hamdy, D. E. Neal, J. L. Donovan, and C. Metcalfe, "Developing new age-specific prostate-specific antigen thresholds for testing for prostate cancer," *Cancer Causes & Control*, vol. 29, no. 3, pp. 383–388, 2018. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5834577/
- [22] A. C. Reese, N. Sadetsky, P. R. Carroll, and M. R. Cooperberg, "Inaccuracies in assignment of clinical stage for localized prostate cancer," *Cancer*, vol. 117, no. 2, pp. 283–289, 2011. [Online]. Available: http://onlinelibrary.wiley.com/doi/abs/10. 1002/cncr.25596