EVALUATING THE DIAGNOSTIC BURDEN OF TUMOR LOCALIZATION STRATEGIES FOR MULTI-CANCER EARLY DETECTION TESTS

ABSTRACT NUMBER 769

CHRISTOPHER TYSON[1], ELIZABETH K. O'DONNELL[1], ELLIOT K. FISHMAN[2], VIJAY PARTHASARATHY[1], TOMASZ M. BEER[1]

[1]EXACT SCIENCES CORPORATION, MADISON, WI [2]DANA FARBER CANCER INSTITUTE, HARVARD UNIVERSITY, BOSTON, MA [3]JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE, BALTIMORE, MD

OBJECTIVES

- Cancers for which screening is available generally show shorter time to diagnosis and better outcomes compared to cancers without screening tests.[1,2]
- Blood-based multi-cancer early detection (MCED) tests are being developed to expand the number of cancers that can be detected by screening in adults.[3,4]
- Since MCED tests are capable of detecting cancer arising from multiple organs or tissue types, an approach to localize the tissue of origin (TOO) for individuals with cancer-suspected results is necessary.
- At present, there are two proposed strategies for TOO localization, both of which often trigger additional procedures to complete the diagnostic process:
  1) Upfront neck-to-thigh imaging[5]
  2) Molecular signal classifier[6]
- To better inform test development and clinical utility, we quantitatively assess the relative diagnostic burden of these strategies.

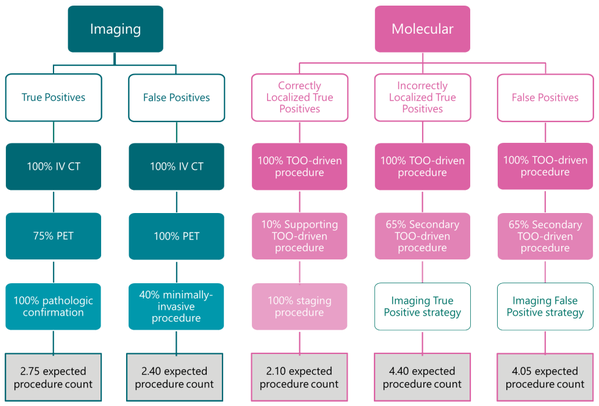
METHODS

In order to compare TOO approaches, we created a measure for diagnostic burden that reflects the total number of diagnostic procedures performed across a range of cancer types and stages, and is influenced by the PPV of the initial MCED test, accuracy of the TOO test, and the clinical decision process following each diagnostic result.

Clinical input and published research were consulted to estimate the number of imaging and invasive diagnostic procedures associated with each diagnostic approach.

- For imaging TOO localization, diagnostic outcomes were separated into true positives and false positives; for molecular TOO localization, diagnostic outcomes were separated into correctly-localized true positives, incorrectly-localized true positives, and false positives.
- In the context of a multi-cancer diagnostic process, the predictive value of single-tissue confirmatory procedures would be low compared to evidence demonstrating relatively high predictive value of advanced radiological imaging[7], and therefore positive calls that are not correctly localized are expected to be resolved by imaging.
- High-level aggregate estimates of procedure sequence were developed using this approach (Fig. 1).

Figure 1. The decision process for estimating the number of procedures associated with each localization strategy and diagnostic outcome. The percentages indicate the anticipated proportion of patients that would be subject to the procedure in question.



CONCLUSIONS

- We developed a method to evaluate the diagnostic burden of MCED TOO localization strategies.
- An imaging-based TOO localization strategy shows better efficiency than a molecular TOO strategy across 95.5% of all possible PPV and TOO accuracies.
- Molecular TOO strategies are likely to require very high PPV or localization accuracy to be more efficient than an imaging TOO strategy.
- A nuanced molecular TOO strategy that incorporates cancer-specific risks and likelihoods may represent a more efficient approach than blanket molecular TOO.

An expression for diagnostic burden is derived as a function of overall test PPV, accuracy of the TOO call, and the number of procedures associated with each diagnostic outcome.

- We begin with the quantitative framework published by Jiao et al[8]:

$$UCT = N\left\{\sum_{i=1}^{k}\rho_i P_i(T^+)[1-L_i(T^+)] + \left(1-\sum_{j=i}^{k}\rho_j\right)(1-S_p)\right\} \quad \text{Eq. 1}$$

$$CD = N\left\{\sum_{i=1}^{k}\rho_i P_i(T^+)L_i(T^+)\right\} \quad \text{Eq. 2}$$

- We arrive at an expression for diagnostic burden (Eq. 3) by combining equations (1) and (2), substituting aggregate test parameters, incorporating a variable for the number of procedures associated with each diagnostic outcome, and reframing the likelihood of each diagnostic outcome using the PPV definition below:

$$PPV = \frac{\rho P(T^+)}{\rho P(T^+) + (1-\rho)(1-S_p)}$$

$$\eta_D = L(T^+)PPV\alpha + (1-L(T^+))PPV\beta + (1-PPV)\gamma \quad \text{Eq. 3}$$

- In Eq. 3, $L(T^+)$ is the TOO accuracy, α is the number of procedures to resolve a correctly-localized true positive, β is the number of procedures to resolve an incorrectly-localized true positive, and γ is the number of procedures to resolve a false positive.
- To calculate the mean and variance across all PPV and TOO accuracies, we employed the following characterizations:

$$\overline{\eta_D} = \frac{1}{dPPV}\frac{1}{dL(T^+)}\iint_0^1 \eta_D(L(T^+), PPV)\,dPPV\,dL(T^+) \quad \text{Eq. 4}$$

$$Var(\eta_D) = \frac{1}{dPPV}\frac{1}{dL(T^+)}\iint_0^1 \left(\eta_D(PPV, L(T^+)) - \overline{\eta_D}\right)^2 dPPV\,dL(T^+) \quad \text{Eq. 5}$$

- We also derived a breakeven equation to assess if and when one TOO localization strategy is more or less burdensome than the other.

$$\eta_{Dmol} = \eta_{Dimg}$$

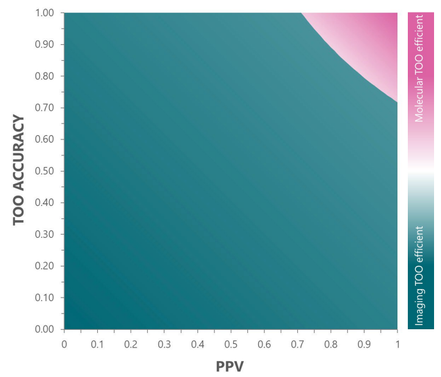
$$L(T^+)PPV\alpha_{mol} + (1-L(T^+))PPV\beta_{mol} + (1-PPV)\gamma_{mol} = PPV\beta_{img} + (1-PPV)\gamma_{img} \quad \text{Eq. 6}$$

- Eq. 6 was used with the base case assumptions for procedure counts to calculate the break even curve as a function of PPV.

Probabilisitc sensitivites analyses were performed to assess robustness of approach and assumptions of the base case.

- Since MCED PPV is likely to fall between 10% and 50%,[5,9] a beta distribution was assigned with parameters α = 3.7 and β = 8.8, which corresponds to a mean of 30%, a 5th percentile around 10% and a 95th percentile around 50%
- With TOO accuracy likely to fall between 80% and 95%,[9] a beta distribution was assigned with parameters α = 46.8 and β = 5.5 which corresponds to a mean of 89.5%, a 5th percentile around 82% and a 95th percentile around 95%
- Procedure counts for each diagnostic outcome were assigned truncated normal distributions parameterized as follows: *mean* is equal to the base case estimate, *min* is equal to 1, *max* is *2(mean)*, and *standard deviation* is (*max-min*)/6
- Stability was assessed by evaluating a threshold change in median joint burden to below 0.1%.
- Diagnostic burden for both strategies were calculated and summarized using descriptive statistics.

Figure 2. The diagnostic burden breakeven curve is plotted and the areas above and below are shaded to reflect the less burdensome TOO strategy.



RESULTS

Mean overall diagnostic burden of imaging TOO strategy was 28% lower than molecular TOO strategy (2.6 vs 3.6, respectively).

- Variance is 0.198 for molecular TOO strategy and 0.010 for imaging TOO strategy.

Molecular TOO strategy is likely to incur lower diagnostic burden for correctly-localized true positives, while an imaging TOO strategy is advantageous for other test outcomes.

- Figure 1 indicates the decision process and resulting diagnostic burden for each diagnostic outcome within each TOO strategy.

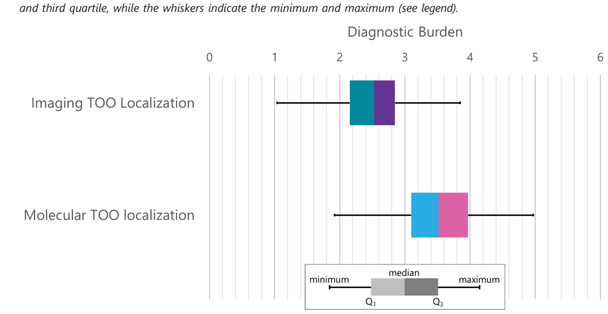
Imaging TOO strategy is expected to be less burdensome than a molecular TOO strategy for 95.5% of all possible PPV and TOO accuracy combinations.

- Figure 2 plots the breakeven curve. The green shaded area below the curve is when an imaging TOO strategy is less burdensome (favorable), while the pink shaded area above the breakeven curve is when a molecular TOO strategy is less burdensome.
- At 90% molecular TOO accuracy, a PPV of 79% is necessary for molecular TOO to have the same diagnostic burden as imaging TOO.

When probabilistically deviating from base case assumptions, imaging TOO strategy maintains efficiency against a more burdensome molecular TOO strategy.

- The probabilistic sensitivity analysis reached stability after approximately 1500 scenarios.
- Imaging TOO delivered a median diagnostic burden of 2.47 (IQR 0.76) against a median molecular TOO burden of 3.49 (IQR 0.87) (Fig. 3).
- In 97.1% of all probabilistic scenarios, a molecular TOO strategy was determined to have a higher diagnostic burden than imaging TOO strategy.

Figure 3. Results of the probabilistic sensitivity analysis are plotted. The boxes represent the first quartile, median, and third quartile, while the whiskers indicate the minimum and maximum (see legend).



REFERENCES

1) Gainullin V, Tong J, Li Y, et al. Characterization of time to diagnosis indicates shorter interval for screenable versus symptom-driven cancers. J Clin Oncol 2022; 40(16) Suppl 10526-10526. doi: 10.1200/JCO.2022.40.16_suppl.10526
2) Ahlquist DA. Universal cancer screening: revolutionary, rational, and realizable. Npj Precis Oncol. 2018;2(1):23. doi:10.1038/ s41698-018-0066-x.
3) Loomans-Kropp HA, Umar A, Minasian LM, Pinsky PF. Multi-Cancer Early Detection Tests: Current Progress and Future Perspectives. Cancer Epidemiol Biomarkers Prev. 2022;31(3):512-514. doi:10.1158/1055-9965.EPI-21-1387
4) Connal S, Cameron JM, Sala A, et al. Liquid biopsies: the future of cancer early detection. J Transl Med. 2023;21(1):118. Published 2023 Feb 11. doi:10.1186/s12967-023-03960-8
5) Lennon AM, Buchanan AH, Kinde I, et al. Feasibility of blood testing combined with PET-CT to screen for cancer and guide intervention. Science. 2020;369(6499):eabb9601. doi:10.1126/science.abb9601
6) Neal RD, Johnson P, Clarke CA, et al. Cell-Free DNA-Based Multi-Cancer Early Detection Test in an Asymptomatic Screening Population (NHS-Galleri): Design of a Pragmatic, Prospective Randomised Controlled Trial. Cancers (Basel). 2022;14(19):4818. Published 2022 Oct 1. doi:10.3390/cancers14194818
7) Lebech AM, Gaardsting A, Loft A, et al. Whole-Body 18F-FDG PET/CT Is Superior to CT as First-Line Diagnostic Imaging in Patients Referred with Serious Nonspecific Symptoms or Signs of Cancer: A Randomized Prospective Study of 200 Patients. J Nucl Med. 2017;58(7):1058-1064. doi:10.2967/jnumed.116.175380
8) Jiao B, Gulati R, Katki HA, Castle PE, Etzioni R. A Quantitative Framework to Study Potential Benefits and Harms of Multi-Cancer Early Detection Testing. Cancer Epidemiol Biomarkers Prev. 2022;31(1):38-44. doi:10.1158/1055-9965.EPI-21-0380
9) Schrag D, McDonnell III CH, Nadauld L, et al. 903O A prospective study of a multi-cancer early detection blood test. Annals of Oncology 2022 Vol. 33 Pages S961. doi: 10.1016/j.annonc.2022.07.1029

DISCLOSURES

This study was funded by Exact Sciences Corporation, Madison, WI. KF is a consultant for Exact Sciences Corp. CT, VP, and TMB are employees of Exact Sciences and have stock ownership.

Presented at: AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING 2023 • ORLANDO, FL, USA • APRIL 14 - 19, 2023