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A BLOOD-BASED CELL FREE DNA TEST TO PRIORITIZE COLONOSCOPY REFERRALS FOLLOWING POSITIVE MOLECULAR SCREENING FOR COLORECTAL CANCER

Harbinger Health

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INTRODUCTION

Colorectal cancer (CRC) is the third most diagnosed cancer in adults in the United States. Effective screening and early detection can significantly reduce mortality. Increased uptake in CRC screening has helped decrease population incidence over the past 40 years. Colonoscopy remains the gold standard in CRC screening and diagnosis but maximal impact on patient outcomes is predicated on its timely application. While non-invasive molecular tests have increased uptake of CRC screening, their modest positive predictive values (PPVs) channel many patients without cancer into constrained endoscopy services. In this setting, cancer risk is heterogeneous, but colonoscopy is often scheduled by referral order rather than likelihood of clinically significant disease. These delays impact patient outcomes; a 4-week treatment delay for CRC patients increases the likelihood of mortality by 12%.[1] Here we describe the application of a blood-based prioritization test designed to resolve molecular-test-positive patients by CRC risk and support earlier colonoscopy for those most likely to harbor cancer. This approach could reprioritize colonoscopy sequence by risk rather than referral order, reducing delays for cancer patients without affecting the number of colonoscopies performed.

Figure 1. Left: Current practice colonoscopy by order of referral. Right: RESOLVE™ approach directs patients towards colonoscopy by order of cancer risk.

METHODS

HHx Cancer Bioassay: Harbinger Health's proprietary methylation biomarkers are informative across multiple cancer indications, including CRC. To interrogate these biomarkers, Harbinger developed a cfDNA NGS assay. Patient cfDNA was isolated from whole blood, bisulfite treated, converted into indexed libraries, enriched for Harbinger's cancer specific biomarkers and sequenced to ≥100X unique median target coverage. The assay was applied to both cfDNA from the CORE-HH clinical study (NCT05435066) and CRC tumor tissue procured from biobanks. All samples were obtained from patients 45 years or older.

Methods

CRC Model Training: A CRC machine learning (ML) classifier was trained with a proprietary feature set on a combination of clinical cfDNA samples and synthetic cfDNA samples, the latter produced with the Harbinger's Synthome™ data generation technique[2]. Synthome™ created in-silico cfDNA admixtures using CRC tumor-tissue-derived NGS data (N=30) and held out non-cancer cfDNA NGS data (N=267), yielding synthetic cfDNA samples (N=309 cancers and N=309 non-cancers). ML scores were computed using nested cross-validation (5-fold, 5 repeats), with decision thresholds determined per-split by inner CV on training-set clinical cfDNA. Final performance is reported on the outer CV, with scores and thresholds averaged per-sample across repeats.

cfDNA CRC Model Performance: Assay performance was evaluated on 1,696 held out cfDNA patient samples, 1,481 from non-cancer patients and 177 from patients with confirmed CRC diagnosis. A 3.4% CRC incidence within the molecular test-positive population was utilized as reported in other publications.[3] We selected two specificity thresholds at 95% and 99% to define the three risk groups for colonoscopy prioritization: urgent 45% CRC PPV , semi-urgent 10% CRC PPV and routine 1% CRC PPV.

Colonoscopy scheduling modeling: The impact of using this prioritization approach on colonoscopies was simulated on a 10,000 person in silico molecular-test-positive cohort. Rank order was calculated under two scenarios. First, patients were randomly assigned a scheduling order, mimicking the current first referred, first screened practice. Second, scheduling order was calculated where patients were screened in an order determined by the Harbinger test, with urgent patients screened first, followed by the semi-urgent and lastly the routine patients. Within each risk group, rank orders were randomly assigned.

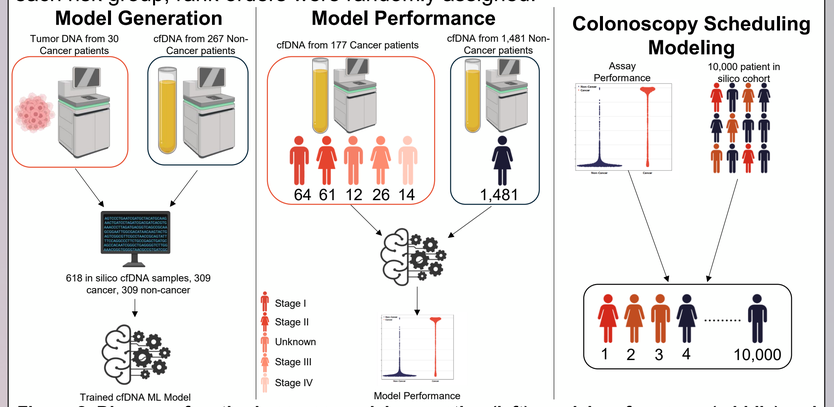

Figure 2. Diagram of methods across model generation (left), model performance (middle) and colonoscopy scheduling modeling (right)

Results

Utilizing the HHx CRC prioritization test most late-stage CRC patients were grouped within the urgent category, and most early-stage patients were within the urgent and semi-urgent groups (see Figure 3 & Table1). As these two groups comprise slightly more than 10% of individuals, this is a significant enrichment. With a representative unit capacity of 80 colonoscopies per day (~400 per week), clearing 10,000 procedures requires ~25 weeks, with a median CRC wait of ~12 weeks under first-come, first-serve schedules. The urgent group would be screened in <2 weeks and contain 41% of early-stage CRC cases (stage I & II) and 76% of late-stage CRC cases (stage III & IV), with an additional 24% of early-stage and 12% of late-stage cases included in the semi-urgent group. When Harbinger risk groups are used to prioritize urgent patients first, followed by semi-urgent patients, 88% of all late-stage and 65% of all early-stage CRC cases would be screened within the first three weeks.

	Percentage of Early-Stage Patients	Percentage of Late-Stage Patients
Urgent	41%	76%
Semi Urgent	24%	12%
Routine	35%	12%

Table 1. Patient composition by risk score

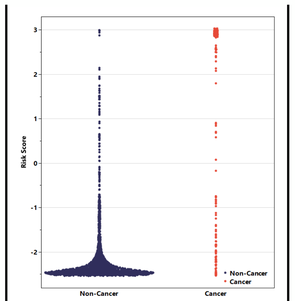

Figure 3. Risk score by Diagnosis

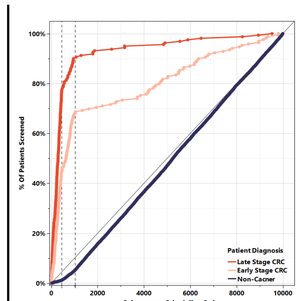

Figure 4. Modeled colonoscopy scheduling order by risk category

CONCLUSIONS

Applying the HHx prioritization approach to patients referred to colonoscopy moves patients most likely to have advanced neoplasia from backlog into dedicated high yield, earlier colonoscopy sessions. Currently the average wait time after a referral for a colonoscopy is ~68 days and patients who experience delays are often not seen for 5 months.[4,5] For CRC patients, and late-stage patients in particular, this delay is a crucial treatment window. Prioritizing patients in need directly affects outcomes, the 12-week median wait time in our scheduling model corresponds with a 39% increase in mortality.[1] Simultaneously, lower cancer risk patients are deferred to routine scheduling without increasing volume. Overall, our approach reallocates fixed colonoscopy capacity according to cancer likelihood rather than referral order, increasing advanced neoplasia yield per procedure, shortening time-to-diagnosis, and offering a lever to align endoscopy throughput with current and future cancer pathway targets.

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Poster diagrams generated using BioRender

DISCLOSURES

This study was sponsored by Harbinger Health. Cambridge, MA

ACKNOWLEDGEMENTS

We gratefully acknowledge all participants for their contributions, without whom this research would not have been possible. We also thank all cross-functional teams for their dedicated efforts that made this work and the resulting data possible.

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