Estimating the Incremental Population Health Impact of a Multi-Cancer Early Detection Test to Complement Existing Screening Among Populations with an Elevated Risk for Cancer with Additional Risk Factors in the United States

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BACKGROUND

- Currently, only single-cancer screening technologies are guideline-recommended, which means populations are screened for one cancer type at a time
- While current cancer screening modalities are considered effective,[1] the majority of cancers do not have guideline-recommended screenings
- The addition of new developments in cancer screening, including multi-cancer early detection (MCED) tests, has the potential to significantly improve upon current guideline-recommended screening, which is the standard of care (SOC) for cancer screening, by identifying cancer types that would otherwise not be found, while minimizing false-positive cases
- Thus far, MCED tests have been demonstrated to be an efficient strategy among those with an elevated risk for cancer (i.e., aged 50+ years)[2]
- The population health impact of MCED tests among patients with additional risk factors for cancer in addition to age has not been assessed

OBJECTIVE

- To estimate the potential efficiency of adding an MCED test to SOC (e.g., breast, cervical, colorectal, lung cancer screening) among individuals aged 50+ years with additional risk factors for cancer (i.e., previous or current tobacco use, family history of cancer, and obesity)

METHODS

- A mathematical model was developed to assess the potential impact of 1 year of screening, including SOC and an MCED test, among individuals aged 50-79 years with additional risk factors,[3] such as previous or current tobacco use, family history of cancer (i.e., having a history of cancer in first degree relatives), and obesity (i.e., body mass index of ≥30) (**Figure 1**)
- The estimated population size of each subgroup was scaled down from the general US population of approximately 107,000,000 individuals aged 50-79 years[4] by deriving the prevalence of each risk factor in the general population aged 50-79 years from the literature[4-5]
- For each risk factor, the standardized incidence rate ratio was derived from the literature[4-5] and calculated using 2020 US Census data as an estimate of the heightened risk of cancer relative to the general population
- For former, ever, and current smokers, the level of low-dose computed tomography (LDCT) uptake and screening eligibility were estimated from published literature[6] to reflect the varying risk levels among these subgroups
- Published estimates of screening uptake and performance[2] were used to model the number of cancers detected by SOC, and the screening performance of an MCED test from a published study[2] was used to model the number of incremental cancers that could be detected by an MCED test
- Outcome measures of screening performance include the cancer detection rate (CDR) (i.e., the number of cancers detected/expected), diagnostic yield (i.e., the number of cancers detected among the total population of screened individuals), and the true-positive:false-positive (TP:FP) ratio, with a high TP:FP ratio (i.e., fewer false-positives [FPs]) indicating higher screening efficiency

RESULTS

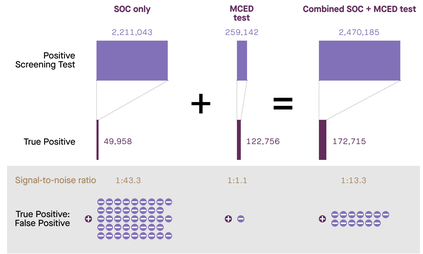
- As depicted in **Figure 3**, for former smokers, the TP:FP ratio of 1:43.3 means that to detect one person with any of the four cancers with SOC screening, approximately 43 people without these cancers may have diagnostic investigations following a screen-positive result. However, the TP:FP ratio of 1:1.1 with an incremental MCED test in former smokers suggests that to detect one person with cancer, approximately one person without cancer may undergo diagnostic investigations, among those with a positive MCED test, indicating high screening efficiency
- Compared to the general population, the TP:FP ratio was higher (i.e., greater screening efficiency) among all subpopulations with elevated risk of cancer receiving SOC only, but particularly for current smokers, followed by those with a family history of cancer and obese individuals (**Table 2**). With the addition of an MCED test, similar trends were seen for current and ever smokers and those with a family history of cancer, and the efficiency was comparable to the general population among obese individuals and former smokers (**Table 2**)
- With SOC only, a slightly smaller proportion of cancers were likely to be detected for all subpopulations, as evidenced by the CDRs compared to the general population, except for former smokers and obese individuals, in which the CDR was similar. With an MCED test, a slightly larger proportion of cancers was likely to be detected for ever and current smokers and those with a family history of cancer and a similar proportion for former smokers and obese individuals (**Table 2**)
- Overall, more cancers were likely to be detected in all subpopulations with an incremental MCED test, with CDRs of approximately 30-40%, thereby representing at least a 3-fold increase in detection rate when compared to those with SOC only (**Table 2**)
- The diagnostic yield was consistently higher for each of the subpopulations compared to the general population, following similar trends of being the highest among current smokers, followed by those with a family history of cancer, obese individuals, and ever smokers with SOC only, and the highest among current smokers, ever smokers, and those with a family history of cancer with the addition of an MCED test (**Table 2**)
- Overall, among the total population of screened individuals, more cancers may be found with the addition of an MCED test vs. SOC only (**Table 2**), given that the diagnostic yield increased by 59-85% for the general population, those with a family history of cancer, obese individuals, and former smokers, and by 112-174% for ever and current smokers

Table 2. Estimates of screening outcome measures for all populations

Population type	SOC only*					Incremental MCED test				
	Total positives**	True positives	Diagnostic yield***	TP:FP ratio	CDR****	Total positives**	True positives	Diagnostic yield***	TP:FP ratio	CDR****
General population	8,255,903	185,666	2.71	1:43.5	15%	990,233	461,427	4.31	1:1.1	37%
Former smokers	2,211,043	49,958	2.73	1:43.3	15%	259,142	122,756	4.45	1:1.1	37%
Ever smokers	3,695,685	89,182	2.96	1:40.4	14%	509,776	284,617	6.29	1:0.8	41%
Current smokers	1,492,698	39,397	3.26	1:36.9	12%	250,502	161,730	8.94	1:0.5	49%
Individuals with a family history of cancer	2,947,557	74,956	3.08	1:38.3	14%	404,669	216,914	5.69	1:0.9	40%
Obese individuals	3,160,726	78,340	3.00	1:39.3	15%	393,598	191,801	4.69	1:1.1	37%

MCED, multi-cancer early detection; SOC, standard of care; TP:FP, true-positive:false-positive; CDR, cancer detection rate
*Includes breast, cervical, lung, and colorectal cancer
**Total positives include true positives and false positives
***Diagnostic yield = cancers detected / total population of screened individuals, expressed per 1,000 people
****CDR = cancers detected / cancers expected

Figure 3. Graphical representation of estimated screening outcome measures for former smokers



DISCUSSION

- There may be additional value and greater efficiency when screening a population that is at an elevated risk for cancer relative to the general population, and detecting additional cancers, many of which may be aggressive
- The majority of cancers may be detected with the combined SOC + MCED test, with CDRs exceeding 50% for all populations, except for obese individuals, for which approximately 44% of cancers may be detected
- While there may be more cancers found with an MCED test in the overall population given its size, the relative impact of screening may be greater among certain higher risk populations, to varying degrees
- Among current smokers, which constitutes about 17% of the general population, an incremental MCED test may increase the number of cancers detected by 87% and may detect approximately 35% of the number of additional cancers that would be detected if the MCED test were applied to the entire population
- With the addition of an MCED test, the TP:FP ratio is 50% lower in the general population (1:1.1) compared to current smokers (1:0.5). With SOC only, the TP:FP ratio is slightly lower in the general population (1:43.5) compared to current smokers (1:36.9). Therefore, there is greater screening efficiency among current smokers with the addition of an MCED test
- When an MCED test is added to SOC for obese individuals, the TP:FP ratio is similar to that of the general population, the diagnostic yield is slightly higher, and the CDR is lower. This may suggest that while more cancers may be found within the screened population of obese individuals, there may be slightly less detection overall of one specific type of cancer or a subset of cancers within the obese population
- While numerous other cancer risk factors exist, this analysis focused on the most common ones, for which literature is widely available regarding their prevalence and risk of multiple cancer types

CONCLUSIONS

- Adding an MCED test to current guideline-recommended cancer screening could be an efficient strategy that increases early detection in select subpopulations with an elevated risk for cancer with additional risk factors
- Our findings may provide information to policy makers, payers, and health care providers about how future innovations in cancer screening may improve screening efficiency in select populations with a higher risk of cancer
- Future research is warranted to understand the screening efficiency among other high-risk populations as well as the real-world implications of screening in more enriched populations

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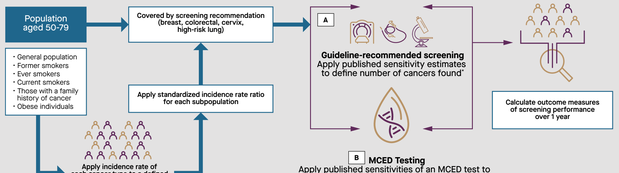
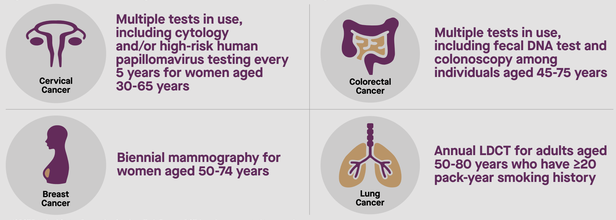
*GRAIL, LLC is currently held separate from Illumina, Inc. under the terms of the Interim Measures Order of the European Commission dated 20 October 2021.

Figure 1. Methodology to estimate the screening performance of guideline-recommended screening with the addition of an MCED test



CDR, cancer detection rate; MCED, multi-cancer early detection; SOC, standard of care; TP:FP, true-positive:false-positive
*Calculated by multiplying the number of cancers covered by each screening type, adherence to that screening guideline, and the sensitivity of the screening modality
**Calculated by multiplying the cancers not detected by current SOC by the sensitivity of an MCED test for that cancer type, and adherence to MCED testing

Figure 2. Current USPSTF guideline-recommended screening



USPSTF, United States Preventive Services Task Force; LDCT, low-dose computed tomography

Table 1. Prevalence of, and risk of cancer among, subpopulations with an elevated risk of cancer and the general US population

Population*	Prevalence	Standardized incidence ratio**
General population aged 50-79 years	100% (n=107,000,000)	1.00
Former smokers[4]	25.8%	1.23
Ever smokers[4]	42.7%	1.63
Current smokers[4]	16.9%	1.24
Individuals with a family history of cancer[3]	35.6%	1.03
Obese individuals[4]	38.2%	1.16

*These estimates reflect the prevalence of, and risk of cancer among, subpopulations with an elevated risk of cancer among those aged 50-79 years, with the exception of those with a family history of cancer, which included all adult individuals
**Incidence of cancer in a subpopulation relative to that in the general population