Appendix

Exhibit 1. MCED Test Features and Relevant Clinical and Payer Implications

MCED Test Features	Potential Clinical Implications[1]	Private Payer Implications	Medicare Implications
Requires adaptation of "one test, one cancer" evidentiary framework for evaluating clinical utility	• Benefits/harms differ by tumor site • Increase CDR because of reliance on aggregate prevalence of rare and common cancers • Impact on survival and patient QoL requires large studies • Simple blood draw facilitates screening compliance/accessibility • Concerns re overdiagnosis, lead time bias, false positives	• Cancer detection insufficient; need evidence of net patient benefit • Benefits of test depends on cancer types/stages detected and differences in stage-specific treatment outcomes and costs • May wait for practice guideline groups to independently assess clinical utility before covering	• No defined benefit category for MCED screening • Legislation introduced in US Congress to include coverage of FDA approved tests; uncertain whether bill will pass
Screening tests have unique coverage requirements	• Risk/benefit evaluation very stringent for presumably cancer-free patients • Typically require evidence of impact of screening on cancer-specific mortality • USPSTF review of new screening tests represents high evidence bar	• Coverage for follow-up diagnostics varies by payer and may lead to substantial out-of-pocket costs for patients • Adds to concerns re costs of false positives, overdiagnosis • USPSTF A or B rating makes screening test a contractual benefit	• Medicare can only cover new prostate or CRC screening tests without specific enabling legislation or USPSTF recommendation A/B • All screening tests require CMS National Coverage Decision
Not a substitute for current screening modalities	• Added to current SOC screening interventions that have varying testing recommendations • Retest interval for MCED tests may be every 1-2 years • May decrease compliance with SOC screening	• Adds to budget impact • Harms of SOC interventions well-defined; harms for MCED may differ by tumor site • Lack of clinical utility data compared to SOC screening likely to be a reason for coverage denial	• One path to coverage is USPSTF recommendation A or B • Likely to require FDA approved test for coverage • May require legislative changes to cover new screening test
Large average risk population (ages ≥ 50 years) eligible for MCED testing	• Demand likely to be high, but will lead to screening paradigm shift requiring extensive public education • May improve compliance with cancer screening due to ease of use • PCPs will be main prescribers of tests, requiring education re	• Shifts more patients from "healthy" to cancer diagnosis in short-term • Self-insured employers may request insurers to cover testing given potential direct and indirect cost impacts • Payers and employers generally may restrict test access initially to high-risk subgroups	• Higher PPV in Medicare population given cancer risk increases with age, but also potentially higher net expenditures if substantial survival benefits are realized

	test interpretation and specialty f/u referrals	because of concerns re insurance premium increases	
Patient access will require payer coverage to avoid inequities in screening and potential disparities in cancer outcomes	• Individuals at greatest risk of missed cancers may be least likely to be able to pay out-of-pocket • May exacerbate existing disparities in cancer outcomes	• In early stages of adoption, IDN's may offer MCED tests at no or reduced cost as market differentiator and in exchange for data sharing (e.g., MCED registry) with test developers	• CMS may pursue access for all Medicare beneficiaries in long-term, but legislative realities will constrain access in near-term • Medicare Advantage plans can choose to offer access to their members
Economic impact of testing	• Depends on test price and testing interval • May identify many new cancers in initial years of adoption but at earlier stages when treatment costs are lower than for metastatic disease	• Major barrier for coverage – may significantly increase premiums for everyone in short term • May be less influenced by CE data given member turn-over	• CBO will evaluate budget impact for Medicare if MCED tests become a covered benefit • Long-term benefits (improved survival, QoL) consistent with Medicare's mission

[1]Not an exhaustive list; potential implications developed based on published information

Abbreviations: CBO – Congressional Budget Office; CDR – cancer detection rate; CE- cost-effectiveness; CMS – Centers for Medicare and Medicaid Services; CRC – colorectal cancer; FDA – Food and Drug Administration; IDN – integrated delivery network; MCED – multi-cancer early detection; PCP – primary care provider; PPV – positive predictive value; SOC – standard of care; QoL – quality of life; USPSTF – United States Preventive Services Task Force.