# The Multi-Cancer Early Detection Test Era: Are we ready for it?

**Kelsey A. Klute, MD**
**Associate Professor**
**Medical Oncologist - UNMC**


1

Disclosures

- Agenus, Oncolys – consultant
- NCCN – Speaker
- AIM Immunotech, Cardiff Oncology – Research (institutional)

Off-Label Use

## Off-Label Use

No MCED tests are currently FDA approved.

Data to be presented is peer-reviewed.

2

# Objectives

1. Understand the basics of multicancer detection tests including how they perform in an average risk population
2. Discuss limitations of multicancer detection tests, including implementation challenges.
3. Discuss how to counsel patients about multicancer detection tests
4. Explore potential advantages and opportunities for research and cancer prevention which leverage multicancer detection tests

3

## Recommended cancer screening for the average-risk individual

**(USPSTF)**


Mammography


Cytology and HPV testing

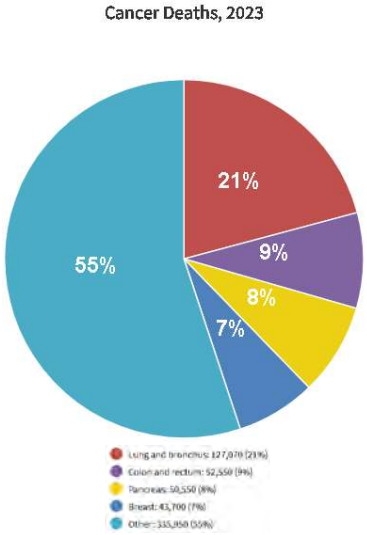

Stool-based test, colonoscopy, CT colonography


Low dose CT (if 20+ pack year smoking history)

**70% of cancer deaths are cause by cancers without recommended screening.**
cancer.org

4

# "Uncommon Cancers" in the US




Seer.cancer.gov

- Breast, lung, prostate and colorectal cancer account for ~50% of new cancer cases in the US.
- Most of the cancer deaths in the US are cause by "other + pancreas" cancer (63%).
  - No highly effective screening modalities exist.

**Though cancer is common, most individual cancer types are relatively rare.**

5

# Needle in a haystack: The challenge of screening for uncommon cancers

Pancreas cancer as an example:

- Hypothetical US population of 64.5 million people age ≥ 55;
  - Pancreas cancer prevalence: ~0.06%
- Hypothetical pancreatic cancer screening test
  - Sensitivity 99%
  - Specificity 99%

| | Patients with pancreas cancer | Patients without pancreas cancer |
|---|---|---|
| Positive test | 35,739 (99%) | 644,639 (1%) False-positive rate |
| Negative test | 361 (1%) | 63,819,261 (99%) |
| All patients | 36,100 | 64,463,900 |

6

# Aggregate prevalence

- **Cancer is common, but individual cancer types are relatively rare.**
- **A single test that detects multiple cancers benefits from the aggregate prevalence of all target cancers.**
  - **↑ positive predictive value**

7

# MCED tests represent a *potential* game changer for cancer control

| Current | Universal |
|---|---|
| *Single-organ screening tests* | *Multi-organ detection tests* |
| - Excludes most cancer types | -Simultaneous multi-organ detection |
| - Multiple modalities | -Potentially includes all cancers |
| - Inefficient | - Single modality |
| - Costly | - Efficient, easily integrated into primary care |
| | - Potentially cost-saving |

Precision Oncology (2018) 2:23 ; doi:10.1038/s41698-018-0066-x

8

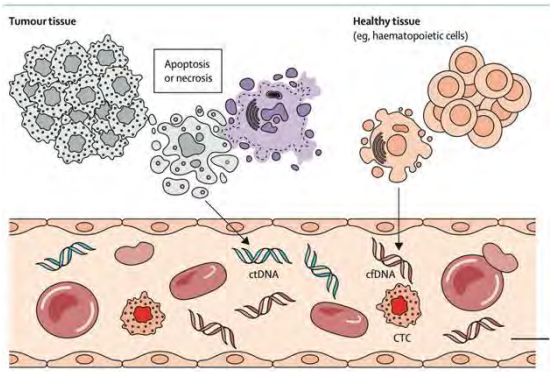
# Multi-Cancer Early Detection (MCED) Tests

- Advances in genomic testing have lead to the development of blood-based cell-free DNA based multicancer detection tests
- Noninvasive tests designed to determine whether and where in the body a person has cancer
- Potential advantages of MCED tests:
  - Improved efficiency and convenience compared to conventional screening
  - Less risk compared to whole body imaging
  - May detect cancers not detected by conventional screening
- Designed to screen for multiple cancer types using a blood sample
  - Commercially available: Galleri (Grail)
  - Coming soon (likely): CancerSEEK/CancerGUARD (Exact Sciences) , OverC (Burning Rock), others

9

# Most MCED tests use ctDNA to detect the presence of cancer

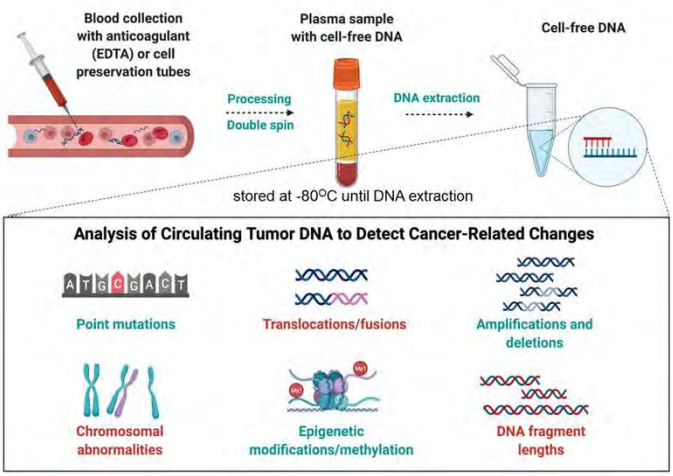
- Fragments of DNA are released into circulation by diseased and normal cells following cell death
- Most cell-free DNA (cfDNA) originates from hematopoietic cells in a healthy adult
- Fragments of DNA found in the cell-free component of whole blood
  - Released by diseased and normal cells
- ctDNA = fragments of tumor DNA released into circulation




Loft M et al. Lancet Gastroenterol Hepatol, 2023.

10

# MCED tests aim to detect cancer-specific and tissue-specific genomic changes in ctDNA

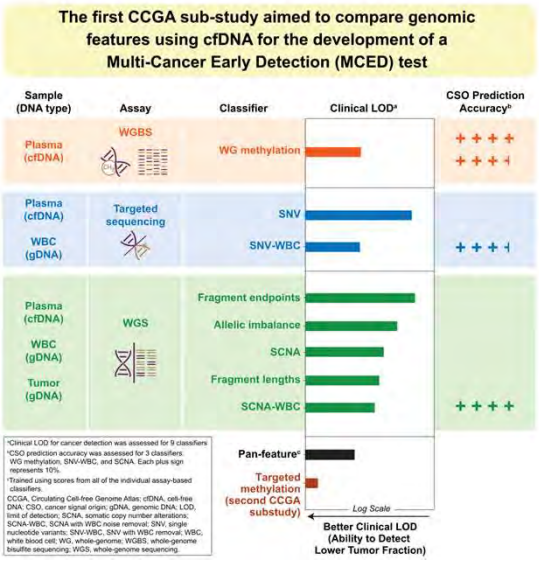



Loft M et al. Lancet Gastroenterol Hepatol, 2023.

11

# Case study: Galleri MCED Test

- The Galleri MCED test is designed to detect cancer-specific DNA methylation patterns from cfDNA shed by tumors into circulating blood
  - Measures the extent and location of DNA methylation patterns → specific to cancer + cancer type
  - If cancer signal detected, predicts signal of origin using methylation signature
  - Developed and validated in the Circulating Cell-Free Genome Atlas (CCGA) study
- Designed to increase the overall cancer detection rate
  - Not designed to specifically detect any individual cancer type

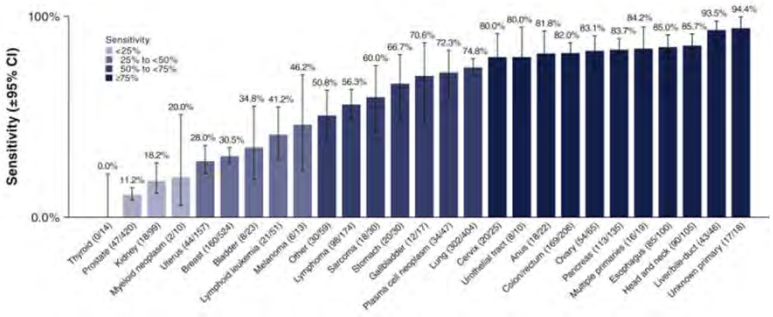


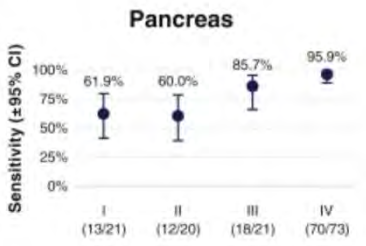

Jamshidi A et al. Cancer Cell, 2022.

12

## Case study: Galleri MCED Test

- Preferentially detects more aggressive tumors
  - Highly proliferative tumors shed more DNA
  - *May* address the problem of overdiagnosis of indolent cancers
  - *Aggressive tumors have a shorter duration in early stage disease – may detect aggressive "interval cancers" at a late stage*




Jamshidi A et al. Cancer Cell, 2022.

13

## Blood-based tests for multicancer early detection (PATHFINDER): a prospective cohort study

*Deb Schrag, Tomasz M Beer, Charles H McDonnell III, Lincoln Nadauld, Christina A Dilaveri, Robert Reid, Catherine R Marinac, Karen C Chung, Margarita Lopatin, Eric T Fung, Eric A Klein*

- Prospective cohort study at 7 sites in the US – Dec 2019 – Dec 2020
- Primary objective: time to diagnostic resolution following a positive MCED test + extent of testing pursued
- Eligible patients were age 50+, had no known or suspected cancer at the time of enrollment and any prior cancer treatment was completed at least 3 years prior
  - Additional risk cohort: smoking history, cancer predisposition syndrome, personal history of cancer
- Procedures:
  - MCED blood test: Galleri – 15d turnaround, results to physician + patient
  - Binary result: cancer not detected or detected + signal of origin prediction
  - Workup left to the discretion of the treating physician
  - End-of-study cancer assessment at 12 months
- Analysis plan:
  - No prespecified hypothesis

Shrag D et al. Lancet , 2023.

14

## Blood-based tests for multicancer early detection (PATHFINDER): a prospective cohort study

Enrolled 6662 participants between Dec 2019 – Dec 2020

- 99% evaluable, 99% had an analyzable MCED result
- 56% had additional risk factors
- 92% white, 64% college degrees
- 4% current smokers
- 92% up-to-date on CRC screening, 81% up-to-date on breast cancer screening

| | Aged ≥50 years with additional risk (n=3681) | Aged ≥50 years without additional risk (n=2940) | Total (n=6621) |
|---|---|---|---|
| Age, years* | 64·0 (58·0–71·0) | 61·0 (55·0–67·0) | 63·0 (56·0–70·0) |
| Age group, years | | | |
| 50–64 | 1858 (50·5%) | 1933 (65·7%) | 3791 (57·3%) |
| 65–79 | 1637 (44·5%) | 931 (31·7%) | 2568 (38·8%) |
| ≥80 | 186 (5·1%) | 76 (2·6%) | 262 (4·0%) |
| Sex | | | |
| Female | 2393 (65·0%) | 1811 (61·6%) | 4204 (63·5%) |
| Male | 1288 (35·0%) | 1129 (38·4%) | 2417 (36·5%) |
| Race or ethnicity | | | |
| Asian† | 39 (1·1%) | 90 (3·1%) | 129 (1·9%) |
| Hispanic | 66 (1·8%) | 68 (2·3%) | 134 (2·0%) |
| Non-Hispanic Black | 44 (1·2%) | 46 (1·6%) | 90 (1·4%) |
| Non-Hispanic White | 3441 (93·5%) | 2630 (89·5%) | 6071 (91·7%) |
| Other‡ | 28 (0·7%) | 38 (1·3%) | 66 (1·0%) |
| Missing | 63 (1·7%) | 68 (2·3%) | 131 (2·0%) |
| BMI, kg/m² | | | |
| <18·5 | 32 (0·9%) | 18 (0·6%) | 50 (0·8%) |
| 18·5 to <25·0 | 1045 (28·4%) | 956 (32·5%) | 2001 (30·2%) |
| 25·0 to <30·0 | 1297 (35·2%) | 1039 (35·3%) | 2336 (35·3%) |
| ≥30·0 | 1264 (34·3%) | 887 (30·2%) | 2151 (32·5%) |
| Other or missing | 43 (1·2%) | 40 (1·4%) | 83 (1·3%) |
| Education | | | |
| Less than high school | 50 (1·4%) | 15 (0·5%) | 65 (1·0%) |
| High school graduate | 345 (9·4%) | 150 (5·1%) | 495 (7·5%) |
| Some college | 1060 (28·8%) | 645 (21·9%) | 1705 (25·8%) |
| College graduate | 2176 (59·1%) | 2100 (71·4%) | 4276 (64·6%) |
| Other or missing | 50 (1·4%) | 30 (1·0%) | 80 (1·2%) |
| Smoking status | | | |
| Current smoker | 268 (7·3%) | 0 | 268 (4·0%) |
| Former smoker | 2229 (60·6%) | 0 | 2229 (33·7%) |
| Non-smoker | 1184 (32·3%) | 2940 (100%) | 4124 (62·3%) |
| Eligible for lung cancer screening§ | 223 (6·1%) | 0 | 223 (3·4%) |
| Previous cancer history | 1622 (44·1%) | 0 | 1622 (24·5%) |
| Cancer predisposition | 425 (11·5%) | 0 | 425 (6·4%) |
| Up to date with standard cancer screening before MCED testing | | | |
| Colorectal cancer¶ | 2404/2628 (91·5%) | 2088/2260 (92·4%) | 4492/4888 (91·9%) |
| Breast cancer‖ | 1504/1930 (77·9%) | 1350/1617 (83·5%) | 2854/3547 (80·5%) |

Shrag D et al. Lancet , 2023.

15

## Blood-based tests for multicancer early detection (PATHFINDER): a prospective cohort study

Results:

- Cancer signal detected in **92 (1.4%)** of 6662 participants
  - True positives: **35 (38%)** of the 92
  - False positive: **57 (62%)**
- 6235 (95.5%) of 9529 were true negatives
  - **86 (1.3%)** were false negatives - most new cancers diagnosed in false negatives were stage I-II n=55 (73%)
  - N=208 (3.2%) did not have a cancer status at the end of the study
- Within 12 months from enrollment, **122 cancers** diagnosed in 121 participants
  - 35 (29%) with a cancer signal detected by MCED
  - 38 (31%) detected through routine screening
  - 48 (40%) clinically detected
- Of the 25 true positive MCED tests:
  - 28 (80%) new cancers; 6 (17%) recurrent cancer; 1 (3%) had both
  - 24 (69%) in the additional-risk cohort

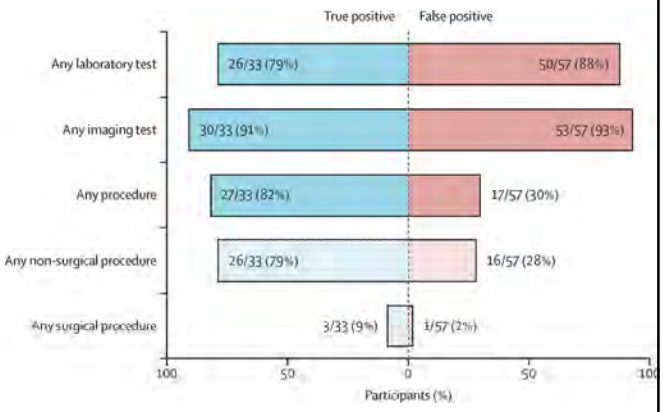
Shrag D et al. Lancet , 2023.

16

## Blood-based tests for multicancer early detection (PATHFINDER): a prospective cohort study

Diagnostic Workup:

- Median time to diagnostic resolution: 79 days
  - True positives resolve more quickly than false positives (57 vs. 162 days).
- Diagnostic testing if cancer signal detected:
  - Lab tests: 84%
  - Imaging: 92%
  - 53% had more than one imaging study
    - PET-CT 61%, CT 39%, MRI 21%
  - Procedure: 49%

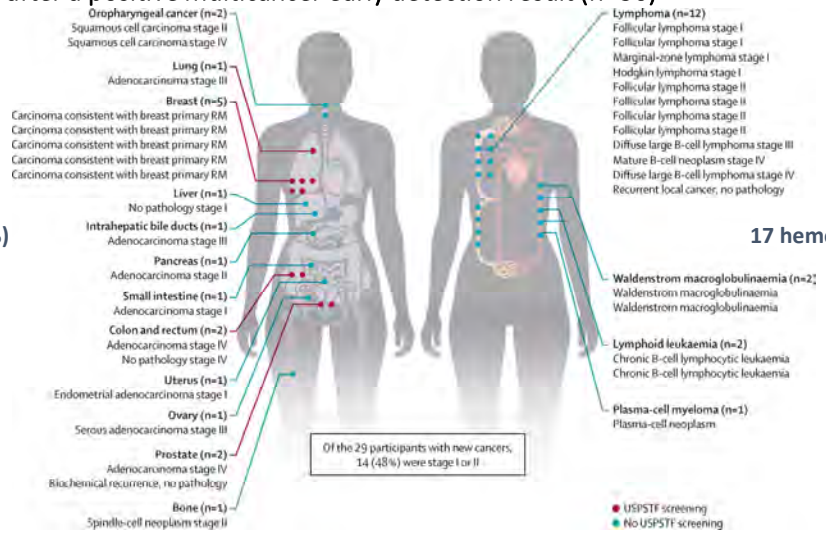



Shrag D et al. Lancet , 2023.

17

## Blood-based tests for multicancer early detection (PATHFINDER): a prospective cohort study

Cancers diagnosed after a positive multicancer early detection result (n=36)




**19 solid tumors (53%)**

**17 heme malignancies (47%)**

**26 (74%) identified a tumor type that does not have a USPSTF screening recommendation**

Shrag D et al. Lancet , 2023.

18

## Blood-based tests for multicancer early detection (PATHFINDER): a prospective cohort study

Test Performance

| | Overall (n=6621) | With additional risk (n=3681) | Without additional risk (n=2940) |
|---|---|---|---|
| **Positive predictive value** | **38%** | 43% | 31% |
| **Negative predictive value** | **98.6%** | 98.5% | 98.8% |
| **Specificity** | **99.1%** | 99.1% | 99.1% |
| **Yield rate** | **0.53%** | 0.65% | 0.37% |
| **Number needed to screen** | **189** | 153 | 267 |
| **First CSO correct** | **85%** | 87% | 82% |
| **First or second CSO correct** | **97%** | 100% | 91% |

***True sensitivity is unknown. Sensitivity based on known cancers = 29% (35/121) – actual sensitivity likely < 29%.***

Shrag D et al. Lancet , 2023.

19


## PATHFINDER study: My Takeaways

- Cancer screening using the Galleri test is feasible. This MCED test detects cancer, site prediction is relatively accurate.
- Are the results generalizable?
  - High rate of baseline adherence with recommended cancer screening
  - Lack of socioeconomic/racial/ethnic diversity
- MCED resulted in earlier cancer diagnosis in 35 cancers
  - 35 of 6662 patients (0.6%)
  - Only 14 of the 29 cancers were stage I-II; only 6 were stage I-II solid tumors
  - **Potential to impact on morbidity/mortality at the population level is unknown.**
- Preferentially detected cancers for which no screening tests exist.
  - **Unlikely to replace current recommended screening procedures.**
  - **Does aggressive biology → higher ctDNA → early detection without mortality benefit?**
- Site of origin is highly predictive
  - Limits scope of diagnostic workup – will payors cover follow-up labs, imaging, procedures?
- Rate of false positives: <1%
  - Only 17 of 6622 underwent a procedure because of a false positive result
  - Could a repeat test or longer follow-up reduce the false positive rate?
- Prevalence testing, brief follow-up period (12mo)
  - Indolent hematological conditions likely overrepresented
  - May not be representative of longer-term screening

20

# MCED tests: More questions than answers

- Further robust research is essential before implementation at a population level.
  - **Mortality benefit: randomized trials are essential to prove mortality benefit, rule out lead time bias**
  - Cost-effectiveness
  - Incidental findings/overdiagnosis – very difficult to measure
  - Combination approaches: HPV testing, stool-based screening, other biomarkers in development
- Other considerations:
  - Cancer detection vs. exclusion
  - How to monitor false positives
  - Test convenience, adherence
  - Value beyond existing approaches to cancer screening and prevention

21

# Galleri MCED Test – Additional studies

Ongoing Studies (Galleri):

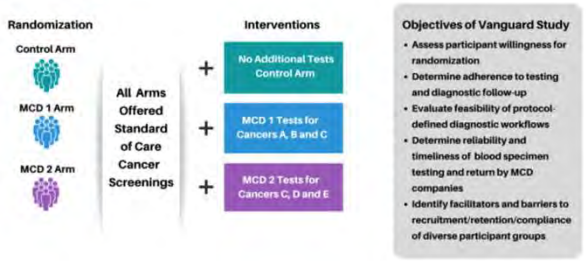
- PATHFINDER2: larger, more diverse population
- NHS Galleri study: 140,000 patients randomized to usual cancer screening vs. usual screening + annual MCED
- REACH (Galleri-Medicare): 50,000 Medicare recipients: MCED + usual care compared to matched controls
- STRIVE: women undergoing mammography
- SUMMIT: validation in individuals at high risk of lung ancer
- REFLECTION: real-world setting
- SYMPLIFY study: MCED testing in individuals with nonspecific symptoms (weight loss, fatigue) Nicholson BD et al. Lancet Oncol, 2023.
  - 5461 patients, 6.7% with cancer, 93.3% without
  - PPV: 75.5%, NPV: 97.6%; sensitivity 66.3% (24% stage I, 95% stage VI), specificity 98.4%

22

# Cancer Screening Research Network

- Clinical trials network established by the NCI
- Goal: evaluate emerging technologies for cancer screening
- Vangard study will launch in 2024: large, randomized multi-cancer detection feasibility study
  - Assess design and implementation for very large randomized trial powered to assess whether multicancer detection tests reduce cancer mortality

## Preliminary Vanguard Study Design




23

# MCED testing for everyone?

- Not yet….
- Benefit unknown: mortality, morbidity, disability
- Impact on health system
  - Cost-effectiveness
  - Cancer disparities

24

## How would I counsel a patient hoping to undergo an MCED test?

**"What are you hoping to achieve with this test?**

Patient education is key.

- MCED tests can detect cancers that we may not have known about for months or years – unclear whether that will benefit you.
  - Pretty good at ruling out cancer *today.* But cancers can be missed by MCED tests.
- False positives are more common than true positives.
  - Any positive result requires more testing – usually imaging, sometimes a biopsy.
- The MCED test does not replace other recommended cancer screenings – I still recommend colonoscopy, mammogram, etc .
- The tests are expensive (~$950) and not currently covered by insurance.

25

## MCED tests: Implementation Challenges

- Patient education, clear communication
  - Should not replace existing cancer screening
  - Anticipation of false positives
- Support for integration into primary care setting
  - Clinician education, resources
- Timely follow-up, which remains an issue with existing screening tests
  - +FOBT/FIT test: only 68% had follow-up within 3 months
    - McCarthy AM et al PROSPR, Am J Prev Med, 2016
  - With MCEDs, follow-up depends on tissue of origin, less streamlined
- Appropriate follow-up for "false positive" test is unknown
- Cost-effectiveness
- How will MCED tests affect existing disparities in cancer screening, mortality?
- **Health care policy and infrastructure must support implementation of MCED**

26

# MCED Tests:
## Questions beyond morbidity, mortality and cost-effectiveness

- Impact of MCED testing on existing cancer disparities
- Are benefits limited to certain cancer types?
  - Morbidity, cost-effectiveness, etc. – will require population level data
- Which test for which patient and how often?
- Emerging technologies: micro RNAs, protein biomarkers
  - Opportunities for combined approaches
- Performance of MCEDs in high-risk populations
- Managing a false positive – repeat test? Interval follow-up imaging?
  - Novel opportunity for prevention, early intervention

27

**Guideline on multi-cancer early detection tests and how to answer patient questions on "liquid biopsies"**

Allison Cushman-Vokoun
Tuesday, November 28, 2023

From: Ray Bergan, MD, Allison Cushman-Vokoun, MD, PhD, Apar Ganti, MD, Joseph Khoury, MD, Kyle Skiermont, PharmD, Julie Vose, MD, MBA, Kelsey Klute, MD

Based on current data, Nebraska Medicine does not recommend broad use of these screening tests at this time. If patients are insistent on obtaining this test, and you believe it to be indicated, or if you have a patient with a positive result, please contact the Cancer Risk and Prevention Clinic at 402.559.5600.

28

# The Multi-cancer Early Detection Test Era: Are we ready for it?

***Not yet…***

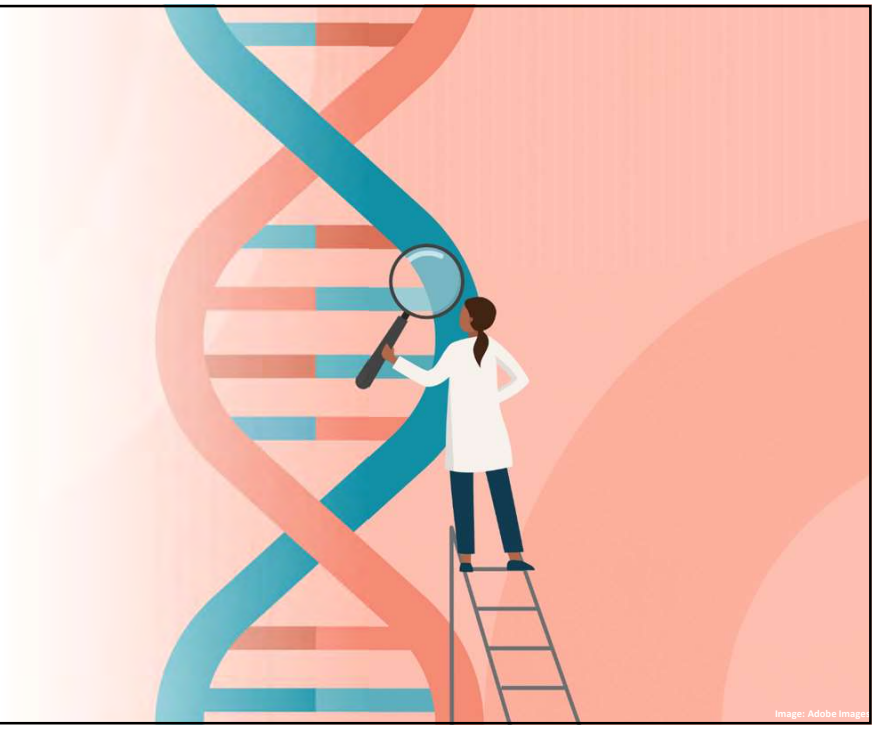

29

# MCED Tests: Conclusions

- Multi-cancer detection tests hold tremendous promise.
  - Potential to dramatically impact field
  - Most people hope to avoid death due to *any* cancer, not one specific cancer.
- "The best test is the one that gets done" does not apply.
  - Current MCED testing is unlikely to replace current recommended cancer screening.
- Critical questions must be addressed before large scale implementation:
  - Mortality, morbidity, disability benefit
  - Cost-effectiveness
  - Payor coverage for initial test, workup
- **The age of MCED tests is upon us: we're not quite ready for it.**


30

# Questions, Discussion




31