Reimbursement Primer & Hot Topics

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Agenda

- Reimbursement primer
  - Coverage
  - Coding
  - Payment

- “Hot” topics
  - Medicare Multi-Cancer Early Detection Screening Coverage Act
  - State biomarker legislation

Coverage

What is required for coverage?

- Medicare: Per Social Security Act 1862(a)(1), “no payment may be made under part A or part B for any expenses incurred for items or services . . . are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member”

- Commercial: “Medically necessary”

- Core evidentiary elements for tests
  - Analytical validity (AV)
  - Clinical validity (CV)
  - Clinical utility (CU)

What are analytical & clinical validity?

- Analytical validity (AV): How accurately and reliably does the test measure the analyte(s) of interest?
  - Elements include (but are not limited to) accuracy, precision, reproducibility, analytical sensitivity (e.g., limits of detection and/or quantitation), analytical specificity (e.g., interfering substances), reference intervals, sample and reagent stability

- Clinical validity (CV): How accurately does the test measure/predict the clinical endpoint(s) of interest?
  - Accuracy with which the test identifies, measures or predicts the presence or absence of a clinical condition or predisposition in a patient

What is clinical utility for tests?

- Providing information?
- Changing physician recommendations?
- **Changing patient management?**
- **Improving "net healthcare outcomes" (effectiveness, safety, health resource utilization*, cost effectiveness*, etc)?**
- Relative to what? Standard of care ("real world" or "best practice")?

Different for different intended uses . . .
so "value" (and hence reimbursement) will (and should) reflect this

Validity ≠ Utility

“Safe & effective” ≠ “Reasonable & necessary”

Regulatory approval ≠ Coverage and payment*

* Exceptions include companion diagnostics (because CV and CU are inextricably linked)

An Example: OncotypeDX Breast

- Analytical validity (AV): How accurately and reliably does the test measure the 21 genes of interest?

- Clinical validity (CV): How well does the score predict the average rate of distant recurrence at 10 years? Chemotherapy benefit?

- Clinical Utility (CU)
  - Decision impact: Does use of the test change how many patients get chemotherapy?
  - Clinical impact: Does use of the test decrease how many patients experience distant recurrence, or increase how many patients benefit from adjuvant chemotherapy, versus the standard of care?
  - Health economic impact: Is use of the test cost-effective versus the standard of care?

Intended use, clinical performance “requirements,” and coverage

- What is the “intended use?”
  - What is being “measured”?
  - Why is it being measured?
  - In whom is it being measured?
  - When (in the care pathway) is it being measured?

- Clinical performance requirements vary with the intended use

- The intended use from CV studies represents the most generous* definition of exactly who should be covered, when, and why
  - Obvious for IVDs, less so for LDTs

* Because study populations from CU studies may be different (and more narrowly defined)

Coding

Welcome to the (coding) jungle . . .

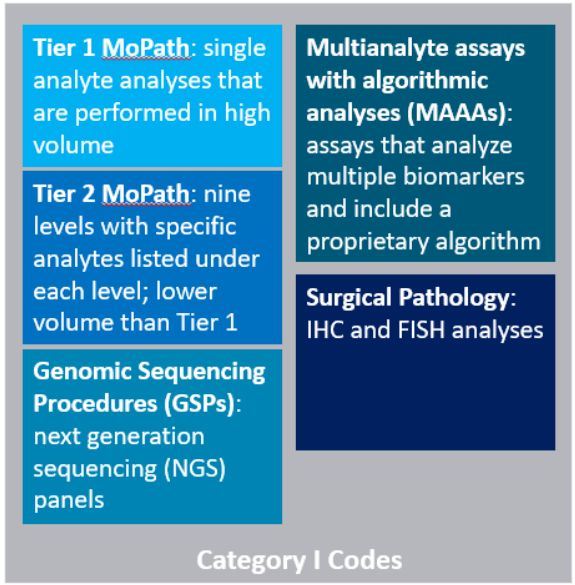
Codes identify services on claims . . .
so having a code does not guarantee coverage and reimbursement (nor should it)

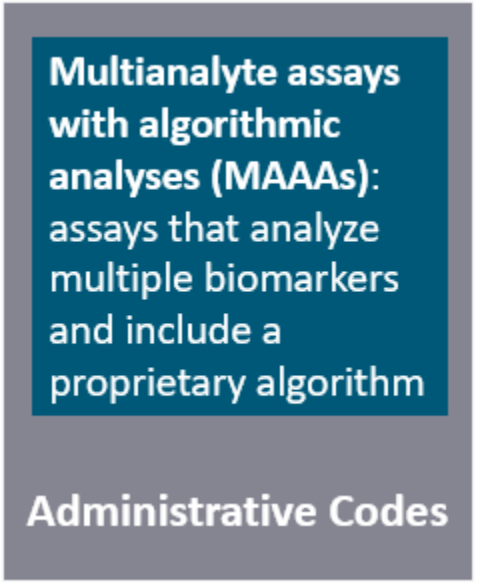
HCPCS Level I Codes: CPT	HCPCS Level II Codes	Z-Code Identifiers
• Maintained by AMA CPT Editorial Panel • Category I codes: published and updated annually • Category III codes (temporary): released semi-annually and published annually • Administrative codes: released tri-annually and published annually • Proprietary Laboratory Analyses (PLA) codes: released quarterly and published annually	• Maintained by CMS HCPCS Workgroup • Permanent codes: established and updated annually • Temporary codes: established and updated quarterly	• Maintained by Change Healthcare • Enable the consistent identification of a unique test • Used by the MolDX program for added specificity and greater clarity in codification of services

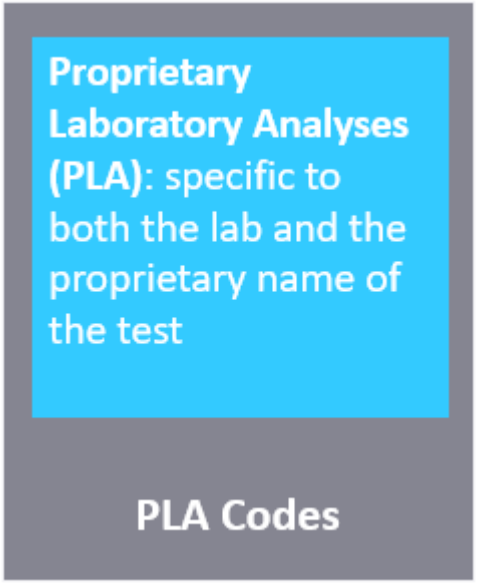
Results in (significant) discrepancies in billing practices and payment among payers

Courtesy of Lauren Feldman, ADVI

Welcome to the (coding) jungle . . . continued







Criteria

Clinical efficacy documented in multiple peer-reviewed publications; utilization requirements

Generally available for patient care

Performed on human specimens; requested by the lab that offers the test

Courtesy of Lauren Feldman, ADVI

Payment

Payment rate-setting methodologies vary by payer

Medicare

- **National**: Reimburses diagnostic laboratory services under one of two payment systems, depending on whether the test involves physician work
  - Clinical Laboratory Fee Schedule (CLFS)
  - Physician Fee Schedule (PFS)

  * National pricing requires a specific CPT or HCPCS Level II code
- **Local**: Priced by individual MACs

Commercial Payers

- Use a variety of methodologies to determine payment rates, which vary based on contracting status ("in-network" vs. "out-of-network")
- Often benchmark payment rates to Medicare

Courtesy of Lauren Feldman, ADVI

CLFS payment rates are set by crosswalk or gapfill

Crosswalk

- Match payment to a test already on the CLFS that it most closely resembles
- Does not account for differences in development costs or resources required to perform test

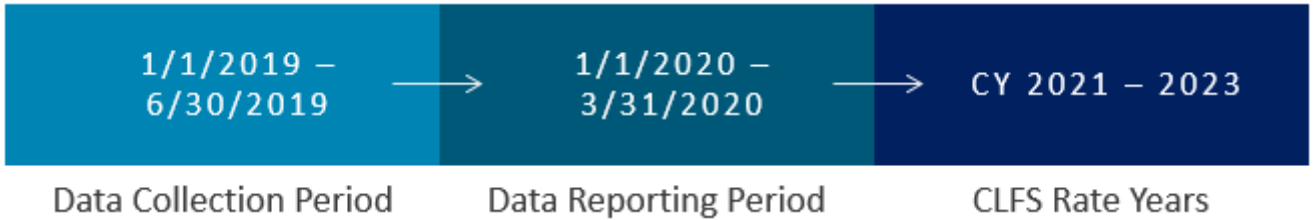
Gapfill

- Used when no comparable, existing test is available
- In the first year, each MAC sets local rates based on:
  - Charges and routine discounts to charges
  - Resources required to perform the test
  - Payment rates determined by other payers
- In the second year, a National Limitation Amount (NLA) is set at the median of local MAC payment rates

Courtesy of Lauren Feldman, ADVI

PAMA changed the CLFS to a market-based system

- Implemented in January 2018, the Protecting Access to Medicare Act (PAMA) attempts to make CLFS payment rates (more) market-based: Rates reflect the weighted median (by volume) of commercial payer rates
- PAMA data collection and reporting cycles are supposed to occur every 3 years but has been repeatedly delayed after 10% year-over-year cuts in 2018-2020. Legislation is currently pending (HR 8188/S 4449) that would require payment rates to be based on "statistical sampling" of commercial payer rates and impose new caps on annual payment decreases/increases.



- In between these cycles, new codes are priced on the CLFS by crosswalk or gapfill

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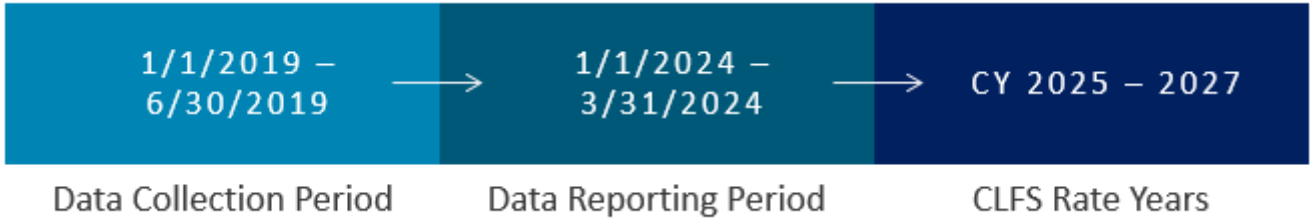

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Courtesy of Lauren Feldman, ADVI

Commercial payer pricing methodologies are less transparent than CMS'

- Can consider cost to perform, health economic "value," cost effectiveness, etc when determining contracted price

- Medicare is statutorily prohibited from considering cost-effectiveness data as an input when pricing

Courtesy of Lauren Feldman, ADVI

“Hot” Topics:
Multi-cancer Screening and Biomarker Testing Legislation

Multi-cancer screening: The unmet need

In 2022, cancers for which USPSTF did not recommend screening in asymptomatic individuals represented ~52% of new cancer diagnoses and ~56% of cancer-related deaths

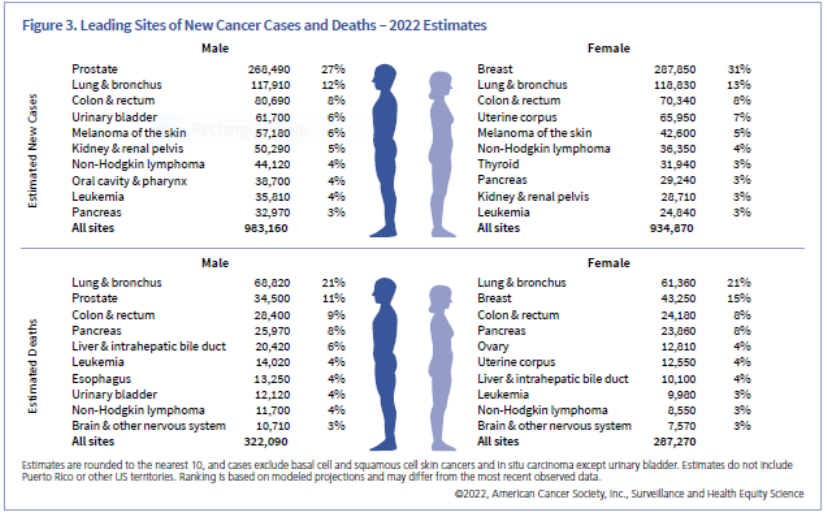


Figure 3. Leading Sites of New Cancer Cases and Deaths – 2022 Estimates

Estimated New Cases

Male			Female		
Prostate	268,490	27%	Breast	287,850	31%
Lung & bronchus	117,910	12%	Lung & bronchus	118,830	13%
Colon & rectum	80,690	8%	Colon & rectum	70,340	8%
Urinary bladder	61,700	6%	Uterine corpus	65,950	7%
Melanoma of the skin	57,180	6%	Melanoma of the skin	42,600	5%
Kidney & renal pelvis	50,290	5%	Non-Hodgkin lymphoma	36,350	4%
Non-Hodgkin lymphoma	44,120	4%	Thyroid	31,940	3%
Oral cavity & pharynx	38,700	4%	Pancreas	29,240	3%
Leukemia	35,810	4%	Kidney & renal pelvis	28,710	3%
Pancreas	32,970	3%	Leukemia	24,840	3%
All sites	983,160		All sites	934,870	

Estimated Deaths

Male			Female		
Lung & bronchus	68,820	21%	Lung & bronchus	61,360	21%
Prostate	34,500	11%	Breast	43,250	15%
Colon & rectum	28,400	9%	Colon & rectum	24,180	8%
Pancreas	25,970	8%	Pancreas	23,860	8%
Liver & intrahepatic bile duct	20,420	6%	Ovary	12,810	4%
Leukemia	14,020	4%	Uterine corpus	12,550	4%
Esophagus	13,250	4%	Liver & intrahepatic bile duct	10,100	4%
Urinary bladder	12,120	4%	Leukemia	9,980	3%
Non-Hodgkin lymphoma	11,700	4%	Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,710	3%	Brain & other nervous system	7,570	3%
All sites	322,090		All sites	287,270	

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

ACS cancer Facts & Figures, 2022

Industry studies

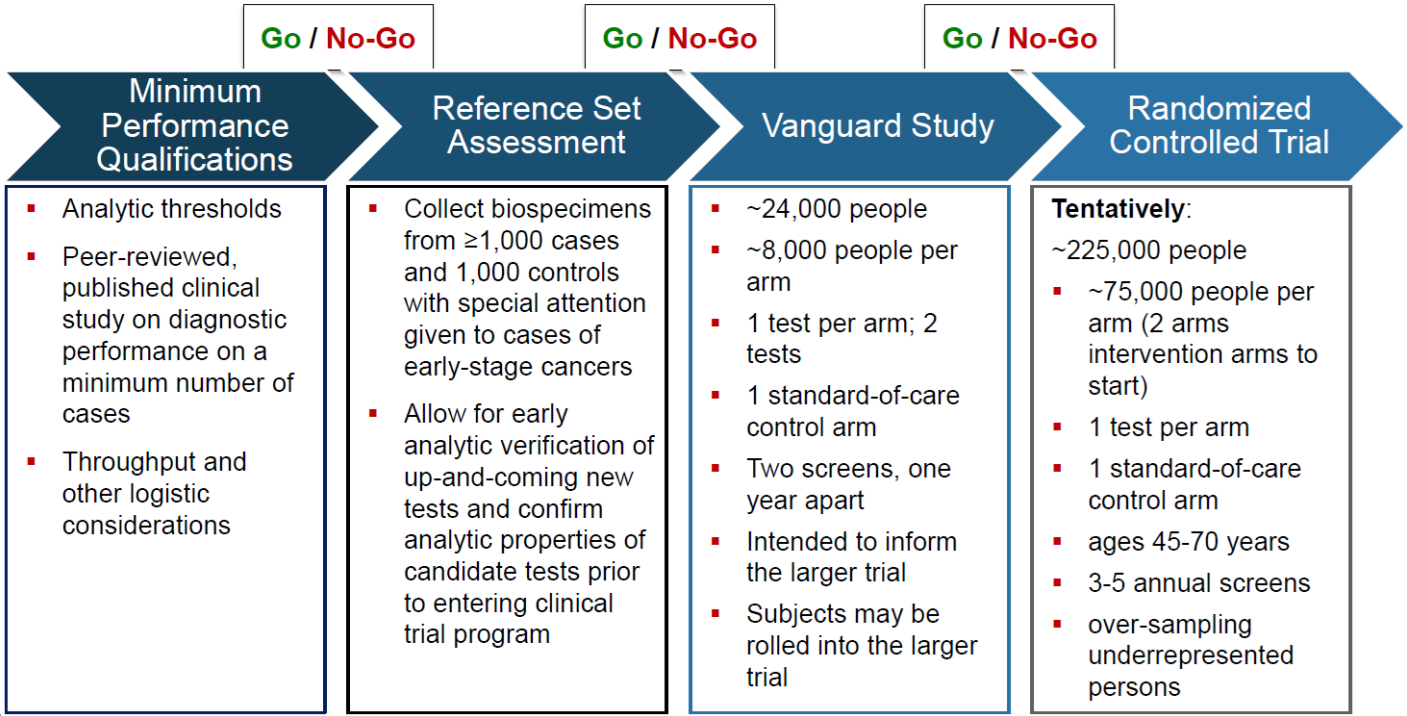
Acronym	Cancer type	Company / ctDNA Assay	Size	Type	Trial identifier	Start	Primary completion	Study completion
PROMISE	Multi	Burning Rock	2,305	Observational	NCT04972201	7/5/2021	12/31/2021	3/31/2022
PREEMPT CRC	CRC	Freenome	25,000	Observational	NCT04369053	5/20/2020	3/31/2022	3/31/2022
BLUE-C	CRC	Exact Sciences / Cologuard	24,000	Observational	NCT04144738	11/15/2019	10/31/2022	10/31/2022
BLUE-C / blood	CRC	Exact Sciences	24,000	Observational	NCT04144751	11/15/2019	10/31/2022	10/31/2022
PREDICT	Multi	Burning Rock	14,026	Observational	NCT04383353	7/21/2020	10/1/2022	3/1/2023
n/a (HCC)	HCC	Genetron Health / HCCScan	4,816	Observational	NCT05343832	11/29/2021	3/5/2023	4/25/2023
CLiMB	Liver	Helio Health	1,600	Observational	NCT03694600	2/4/2019	2/28/2023	5/28/2023
PRESCIENT	Multi	Burning Rock	11,879	Observational	NCT04822792	3/23/2021	3/31/2023	6/30/2023
K-DETEK	Multi	Gene Solutions	1,643	Observational	NCT05227261	4/1/2022	8/1/2023	12/1/2023
ECLIPSE	CRC	Guardant Health / SHIELD	20,000	Observational	NCT04136002	10/8/2019	1/1/2022	1/1/2024
CASCADE-LUNG	Lung	Delfi / DELFI	15,000	Observational	NCT05306288	4/7/2022	3/31/2025	3/31/2025
STRIVE	Multi	GRAIL / Galleri	99,481	Observational	NCT03085888	2/28/2017	6/1/2022	5/1/2025
ALTUS	HCC	Exact Sciences	3,000	Observational	NCT05064553	7/26/2021	7/1/2023	10/1/2025
SHIELD	Lung	Guardant Health / SHIELD	9,000	Observational	NCT05117840	1/13/2022	12/31/2024	12/31/2025
NHS-Galleri	Multi	GRAIL / Galleri	140,000	Interventional	ISRCTN91431511	7/1/2021	2/28/2026	2/28/2026
PATHFINDER 2	Multi	GRAIL / Galleri	20,000	Interventional	NCT05155605	12/8/2021	6/30/2023	7/30/2026
CAMPERR	Multi	Adela	5,280	Observational	NCT05366881	5/3/2022	12/1/2023	12/1/2026
REFLECTION	Multi	GRAIL / Galleri	35,000	Observational	NCT05205967	8/23/2021	8/23/2024	8/23/2028
PREVENT	Multi	Burning Rock	12,500	Interventional	NCT05227534	6/1/2022	3/1/2024	12/31/2028
SUMMIT	Multi	GRAIL / Galleri	13,035	Observational	NCT03934866	4/8/2019	8/1/2023	8/1/2030

Source: Company data, ClinicalTrials.gov, Credit Suisse

NCI studies

CANCER MOONSHOT
PRESIDENT JOE BIDEN

Schema for Step-Wise Validation



Intended use and clinical performance “requirements” for multi-cancer screening and early detection (MSED) tests

- What is the “intended use?”
  - What is being “measured”?
  - Why is it being measured?
    - For screening, post-diagnosis risk stratification, etc?
    - For unscreened and/or screened cancers?
  - In whom is it being measured?
    - Elevated or “average” risk
    - Asymptomatic or symptomatic
  - When (in the care pathway) is it being measured?
    - Upstream, as a replacement for, or downstream of standard-of-care screens (if they exist)

- Clinical performance requirements vary with the intended use

Clinical performance “requirements” are different if screening for different cancers

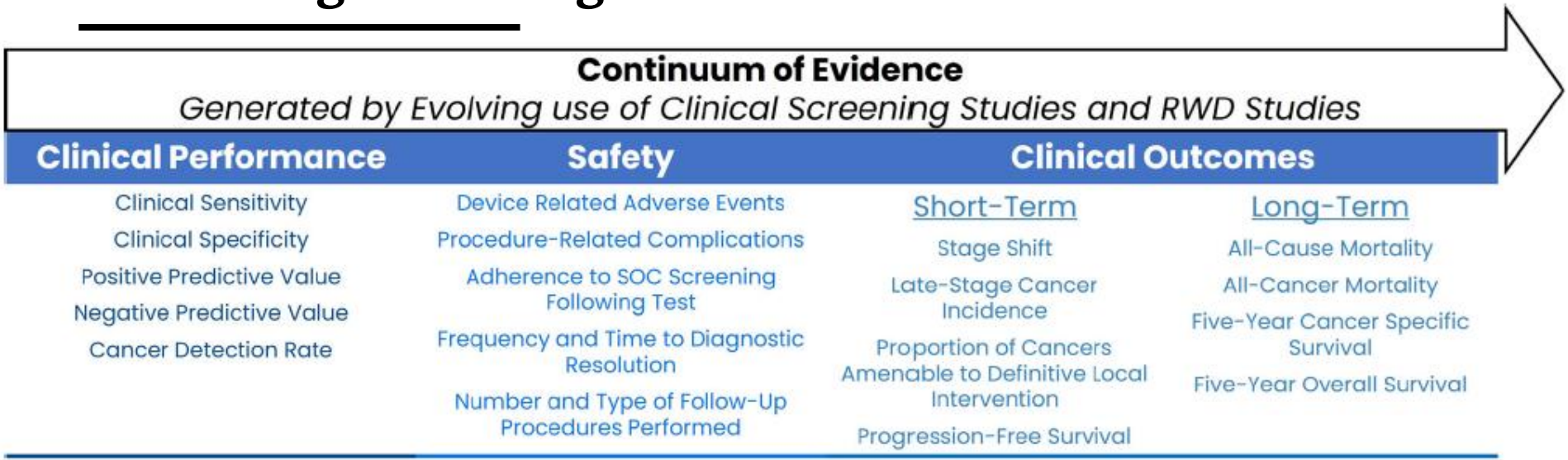
	Colorectal cancer	Breast cancer	Ovarian cancer
USPSTF recommendation	Grade A	Grade B	Grade D
Screening goal	Minimize false negatives	Minimize false positives	Minimize false positives
Final diagnostic confirmation	Colonoscopy	Fine needle aspirate or core biopsy	Abdominal surgery
Target test requirements	High NPV (high sensitivity)	High PPV (high specificity)	Very high PPV (very high specificity)

PMID 34994606

“Requirements” for a multi-cancer screening test

- “Very low” false positive rate in unscreened cancers
- If include screened cancers, comparable or better performance (sensitivity AND specificity) versus the existing standard of care (“adjusted for” real-world adherence?)
- “Very low” tissue-of-origin misclassification (i.e., “very high” localization accuracy)
- Clinical validity and utility established in the intended use population

Clinical utility and surrogate endpoints . . . What is "good enough?"



- How accurate are any of the "short-term" endpoints in predicting the "long-term" endpoints?
- Is this different for different cancers? (Lessons from UKCTOCS and other screening studies)
- How exactly is "stage shift" defined? (Stage 4 to 3? "Late" to "early?")
- Is a decrease in late-stage cancer incidence relative, absolute, or both?

Friends of Cancer Research white paper, 2022

Medicare Multi-Cancer Early Detection Screening Coverage Act

- First introduced as H.R. 1946 on March 16, 2021 and S. 1873 on May 27, 2021; re-introduced as H.R. 2407 on March 30, 2023
- Key provisions
  - Creates a “covered benefit” for MSED tests
  - Requires FDA approval (validity, not utility) for Medicare coverage
  - Test must include “analysis of cell-free nucleic acids” (but allows Secretary to allow other “equivalent” tests)
  - Limits coverage to 1 test per year but can get in addition to standard-of-care screening for breast, cervical, colorectal, lung, and prostate cancer (and vice versa)
- Comments
  - Enables tests to bypass USPSTF review = coverage through legislation, not evidence with uncertain and significant budgetary implications
  - Incorrectly suggests that MSED tests can be “diagnostic” or “confirmatory”

Source: Congress.gov

State legislation for biomarker testing

- Versions passed in AZ, IL, LA, and RI; pending in NY, OH, and WA; vetoed in CA

- Mandates coverage “for the purposes of diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition to guide treatment decisions” for “biomarker testing” when the test has “clinical utility” based on
  - FDA label
  - CMS NCD or MAC LCD
  - Nationally recognized clinical practice guidelines and consensus statements

Source: Triage Cancer

State legislation for biomarker testing: Comments

- Definitions are broad, vague, and/or incorrect (e.g., biomarker, clinical utility, nationally recognized clinical practice guidelines, and consensus statements)

- Conflates validity (“safe and effective”) with utility (“medically necessary”) and ignores inconsistencies among (and “political influence” on) NCDs, LCDs, guidelines, and consensus statements and significant variability in the rigor of their underlying evidence reviews

- Seems to mandate coverage of any test for any purpose with limited (and highly variable) supporting evidence

- Yet another example of leveraging real healthcare disparities to advance coverage for “innovations” of unproven benefit through legislation, not evidence, with uncertain and significant budgetary implications

Thank you.

Questions and comments are welcome.

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