Establishing the Clinical Validity and Utility of Multi-cancer Detection Tests

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Disclosures

- Alberto Gutierrez
  - Consulting: Multiple companies, mostly ad-hoc

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  - Consulting: Natera, Optum Genomics
  - Equity: Freenome

- Opinions expressed herein are my own.

Cumulative performance metrics are not sufficient as study endpoints

- Cancer is not one disease but many
- A diagnosis of “cancer” is not actionable without localization information to guide the subsequent workup
- The accuracy of tissue-of-origin (TOO)/cancer signal origin (CSO) information must be understood to inform the evaluation of benefits and risks

Cumulative versus per-cancer endpoints is a false choice – it should be both

- Focusing only on cumulative statistics (PPV, NPV, Sn, Sp) can obfuscate performance in specific cancers (example of “pan-cancer” or “cancer agnostic” drug approvals?)
  - Based on SEER data, ~50-60% of the PPV of MCD tests may be attributable to USPSTF A/B cancers for which SOC screening exists (~70-80% if one includes prostate)

- Can one use a structure like biomarker tiers for tumor profiling NGS tests?
  - Level 1: Cancers with SOC screening and pre-specified, statistically significant clinical validity (CV) endpoints
  - Level 2: Cancers with statistically significant CV endpoints
  - Level 3: Cancers with only analytical claims

- Can/should one group cancers based on shared follow-up diagnostic procedure? For example, grouping cancers that are diagnosed by endoscopic ultrasound (EUS), colonoscopy, etc?

What is “early” detection?

Cancer Type	Cure Fraction by Stage			
	I	II	III	IV
Liver	31	30	7	2
Pancreas	39	13	4	2
Gallbladder	47	22	20	2
Esophagus	57	39	23	5
Lung	61	37	16	4
Stomach	67	41	27	5
Ovary	71	44	16	3
Urothelial Tract	79	72	56	17
Sarcoma	85	74	50	10
Breast	87	82	57	2
Anus	88	83	69	23
Prostate	88	83	80	47
Lymphoma	90	85	79	72
Cervix	91	75	54	19
Colorectal	91	66	63	7
Bladder	92	66	52	17
Kidney	93	76	68	11
Head/Neck	94	86	75	60
Melanoma	94	74	61	22
Uterus	94	82	65	16
Thyroid	96	94	90	82

Hubbell and Clarke, AACR, 2022

- Localized cancer amenable to local intervention for curative intent = different for different cancers (not stage 1 and 2 for every cancer)
- If the goal of “early detection” is to improve clinical outcomes (however measured), then “early” detection is different for different cancers
- Detection = clinical validity not utility (though it is implied)

Clinical validity for MCD tests: General principles

- In the intended use population
- Pre-specify endpoints and statistical analyses for “any cancer,” and for individual cancers for which one seeks clinical (versus analytical) claims
- Enable enrollment of “elevated risk” individuals based on age and smoking status alone (no known genetic syndromes)
- Clinical truth based on diagnosis of cancer within a pre-specified period of time after specimen collection

Clinical utility and surrogate endpoints for MCD tests: General comments

- To date, no test granted a screening claim by the FDA has performed an interventional study for pre-market authorization, but times have changed . . .

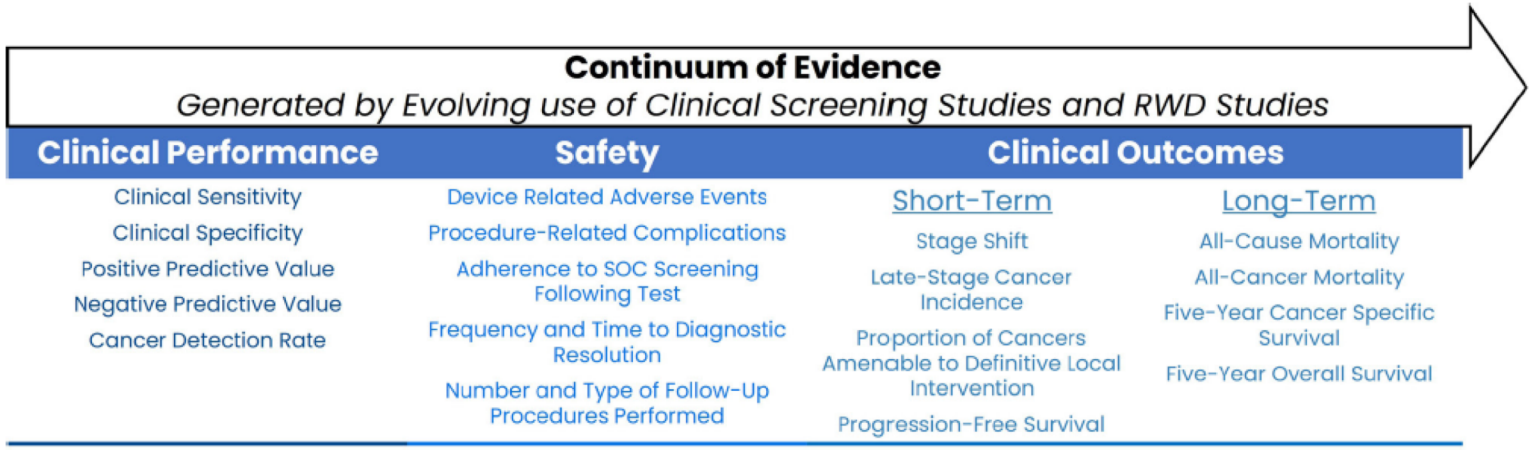
- The strength of association between proposed surrogate endpoints (e.g., decrease in late stage cancer incidence or “stage shift”) and “hard” endpoints (e.g., cancer-specific and overall mortality) varies greatly . . .
  - At best, varies on a cancer-specific basis (e.g., late stage cancer incidence and cancer-specific mortality in USPSTF A/B cancers like colorectal versus USPSTF D cancers like ovarian)
  - At worst, does not exist for some cancers (e.g., ovarian) based on available data
  - Needs to be defined clearly and consistently
    - What is “early” and “late” for each cancer?
    - Are changes relative, absolute, or both?

- A focus solely on cancer-specific let alone overall mortality misses the very real benefits that may come from decreased morbidity with accurate “early” detection

Clinical utility and surrogate endpoints for MCD tests: General comments

- If at least part of the motivation to use aggregate measures for CV is to “accelerate innovation” and benefit patients “sooner,” then why not aggregate for clinical utility (CU) endpoints too (e.g. all-cancer morbidity and mortality)?

- If one is going to lower the evidentiary bar for market authorization, then one really must have robust requirements for post-market evidence development and the willingness and ability to enforce timely and rigorous completion of these requirements, up to and including removal from the market if these commitments are not met in a timely manner.



Friends of Cancer Research white paper, 2022

Clinical utility and surrogate endpoints for MCD tests: General principles

- In the intended use population

- Randomize to SOC vs SOC + MCD test

- Collect both surrogate and “hard” endpoints, such as
  - Frequency and time to diagnostic resolution
  - Number, type, and complications resulting from follow-up procedures
  - “Early” and “late” stage cancer incidence at diagnosis (per cancer and aggregated)
  - All cancer and cancer-specific morbidity measures (e.g., QLQ-C30, hospitalization rate, performance status)
  - 5-year all cancer and cancer-specific survival
  - All cancer, cancer-specific, and overall mortality

- We just need to decide where to “draw the line”