Design Considerations for Multi-cancer Detection Tests

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Disclosures

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

- Girish Putcha
  - Consulting: Natera, Optum Genomics
  - Equity: Freenome

- Opinions expressed herein are our own.

MCD tests have different intended uses

- Each with their own clinical performance
- Each with different benefit risk profiles
- Each with different intended use populations
- Each with different prevalence
- Each with a different biological profile and natural history

MCD tests have different intended uses, each with their own clinical performance requirements

- Does the test precede, complement or replace a standard of care (SOC) method of screening?
  - "Pre-screen" ≠ screen
  - How will an MCD test that always leads to a SOC screen regardless of the test result increase adherence to the same SOC screen to which patients are currently not adhering? How will it solve the "cumulative false positive problem" if all individuals regardless of MCD test result must still get the same SOC screen?
  - If the unmet need is cancers for which no screening in the general population exists, then why not design a test focused on only these cancers?

- In what population of patients?
  - Known "high risk" = surveillance (not screening)
  - ≥ 50 yo with no known risk factors for the cancers included in the test? How to operationalize? (Only known genetic risk factors?)

- Those who do not learn from the past . . .
  - Screening is not diagnosis: Lessons from non-invasive prenatal screening
  - "Pan" versus "multi" cancer

Prospectively designed case-control studies using post-diagnostic, pre-treatment samples uniformly overestimate clinical performance

	Lidgard (2013)	DeeP-C (2014)
CRC sensitivity	98% (n = 93)	92% (n = 65)
AA sensitivity	57% (n = 114)	42% (n = 760)
ACN specificity	90% (nominal) (n = 796)	87% (n = 9198)

Degradation in clinical performance has also been observed more recently in both single and multi-cancer studies based on publicly available data

Sources: P130017 SSED, PMID 23639600

Spectrum bias is common in case-control studies . . .

Cancer Stage	Lidgard (2013)	DeeP-C (2014)
I	22%	45%
II	26%	32%
III	33%	15%
IV	8%	6%
Unknown	11%	2%

Final diagnosis of index lesion	Lidgard (2013)	DeeP-C (2014)
CRC	9%	1%
AA	11%	8%
NAA	15%	29%
NEG	64%	63%

Sources: P130017 SSED, PMID 23639600

. . . and can materially impact clinical performance measures

Subtype distribution within AA, NAA, and NEG can materially impact AA sensitivity and ACN specificity

AA Subtype	Distribution	Sensitivity	Category	Distribution	Specificity
2.1	5.2%	69.2%	3	8.1%	81.0%
2.2	33.8%	44.1%	4	4.6%	72.1%
2.3	48.0%	37.7%	5	18.9%	86.2%
2.4	13.1%	42.4%	6.1	19.8%	84.7%
			6.2	48.6%	89.8%

Source: P130017 SSED

This can be done . . .

- Because it is not realistic (or ethical) to get tissue pathology-based confirmation of "clinical truth" (i.e., presence or absence of cancer) for multiple cancer types in every subject in a cohort study, consider use of cancer diagnosis within a pre-specified period of time after specimen collection

- It is possible to design a single prospective cohort study to establish the clinical validity of an MCD test with a study of the size of those that are planned or currently underway