UNITEDHEALTH GROUP

Evidence Expectations for Clinical Tests

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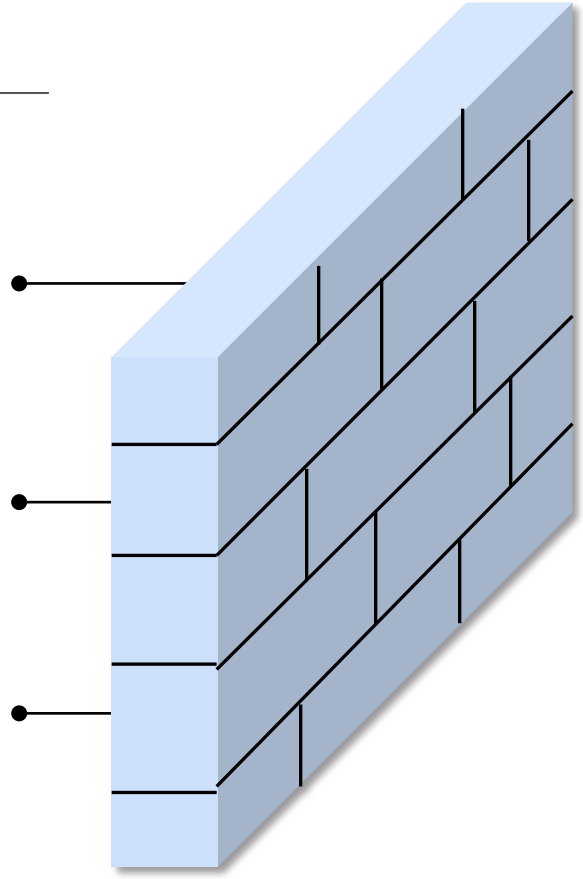
Why does UHG have a genomics team?

Precision medicine continues to face systemic barriers to growth and adoption

Precision Medicine Industry Challenges

1. **Lack of evidence** that the test is valid (it works) and has utility (the results are useful).
2. Confusion and mistrust due to **inconsistent regulatory oversight** and wide variability in the quality and utility of LDTs on the market.
3. Long timelines to generate the evidence needed for coverage and adoption and **investor misalignment** on time and cost expectations.



Technologies languish in an evidentiary limbo slowing the promise of precision medicine and access to transformative technologies

Optum Genomics

Accelerating and incentivizing test quality in precision health.

“Optum Genomics” sits in UHG Enterprise Strategy

Optum Evidence Engine (External-facing)

Consulting service to help test developers understand, obtain, and disseminate the evidence needed to achieve payer coverage and provider adoption.

- Evidence Planning
- Market Access
- Evidence Generation

Test Quality Reviews, White Papers, Policy Support (Internal-facing)

- Creation of quality-based test lists for UHG businesses.
- Enterprise consensus white papers on complex or controversial test types.
- Policy support for IVD/LDT topics
- Utilization management support for Optum Care clinics
- Strategic integration of quality tests into UHG businesses

Multi-Cancer Early Detection White Paper

Liquid biopsy is an exciting technology with potential to impact cancer screening.

At this time, the data on safety and utility of these MCD tests to date are not sufficient to support coverage by the health plan.

There are currently no evidence-based recommendations for use of this test to detect cancers, nor is there consensus regarding management of an individual with a positive test.

These tests should not be used on members, patients, or employees outside of an Institutional Review Board (IRB)-approved clinical trial.

Approach to the White Paper:

- Apply WHO screening criteria to MCD (Wilson and Jungner, 1968. Dobrow, et al, 2018).
- Recommendations for cancer screening test developers.

Wilson, James Maxwell Glover, Gunnar Jungner, and World Health Organization. "Principles and practice of screening for disease." (1968).
Dobrow, Mark J., et al. "Consolidated principles for screening based on a systematic review and consensus process." *Cmaj*190.14 (2018): E422-E429.

Consensus Concerns with Multi-Cancer Screening

Cancer screening should reduce overall mortality from that cancer type. To date, there are 4 tumor types where screening meets this standard (breast, colon, cervix, lung). While screening for additional cancers is conceptually attractive, this evidence standard has not been met.

“Cancer” is not a single disease.

- Different natural histories.
- Different levels of shedding into the blood stream by type and stage.
- Different latent periods with different different optimal testing intervals.
- Different prevalences and different PPV/NPVs.
- Different tolerance for false results based on the technical performance and risk of the recommended confirmatory test.
- Different follow-up care is necessarily based on the cancer site of origin, an analysis of aggregate clinical utility will be difficult to produce and interpret.

Box 1. Wilson and Jungner classic screening criteria (W&J)[5]

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a “once and for all” project.

Recommendations

Select and multiplex cancers with similar characteristics.

Limit the intended use to higher risk individuals and focusing on better performing cancer types.

Specify the site of origin and provide organ-specific predictive values.

Screening tests should be part of a screening *program* to ensure appropriate follow up and treatment.

Pre-Evidence adopters should consider the cost of working up a positive MCED result.

- There are no established evidence-based criteria to allow for imaging solely for the evaluation of a positive screening from an unproven test and may not be covered.
- Workup of an unproven positive blood cancer screening test as the sole indication does not meet medical criteria.
- These tests may be denied unless the employer wishes to grant a benefit exception.

Box 2. Dobrow and colleagues consolidated screening criteria (D)[6]

Disease/condition principles

1. Epidemiology of the disease or condition
2. Natural history of disease or condition
3. Target population for screening

Test/intervention principles

4. Screening test performance characteristics
5. Interpretation of screening test results
6. Post screening test options

Program/system principles

7. Screening program infrastructure
8. Screening program coordination and integration
9. Screening program acceptability and ethics
10. Screening program benefits and harms

Not in the white paper, but may be useful

What about "coverage with evidence determination?"

- Commercial health plans have a contract with their members, a Certificate of Coverage (CoC), that details the benefits and exclusions.
- Experimental or Unproven services are typically excluded.
- CoC's are available on-line.

What about health economic models and costs? Do payers care? Depends on who you ask.

- Medical policy– Typically, no.
- Networks and Contracting– Typically, yes.
- Payer and provider facing products– Typically, yes.

Discussion

Example of PPVs by cancer type

TABLE 4: EXTRAPOLATED PPVS FOR THE GRAIL GALLERI MCED BASED ON CANCER PREVALENCE.

		Weighted Avg PPV		
Canceer Site	**Overall Sensitivity**	**50-59**	**60-69**	**70+**
All Sites	0.4			
Breast	0.305	11.873%	15.041%	17.957%
Cervix Uteri	0.8	0.529%	0.428%	0.404%
Colon and Rectum	0.82	3.266%	4.602%	7.784%
Corpus and Uterus, NOS	0.28	0.499%	1.509%	2.361%
Esophagus	0.85	0.005%	0.024%	0.042%
Hodgkin Lymphoma	0.563	0.262%	0.106%	0.033%
Kidney and Renal Pelvis	0.182	0.283%	0.507%	0.753%
Larynx	?	0.000%	0.000%	0.000%
Leukemia	0.412	0.237%	0.388%	0.678%
Acute Lymphocytic Leukemia	0.412	0.005%	0.001%	0.000%
Liver and Intrahepatic Bile Duct	0.935	0.033%	0.169%	0.067%
Lung and Bronchus	0.748	0.367%	1.380%	2.850%
Melanoma of the Skin	0.462	3.069%	3.627%	4.428%
Myeloma	0.2	0.018%	0.050%	0.080%
Non-Hodgkin Lymphoma	?			
Oral Cavity and Pharynx	?			
Ovary	0.831	0.275%	0.358%	0.365%
Pancreas	0.837	0.025%	0.066%	0.079%
Prostate	0.112	0.845%	7.034%	16.831%
Stomach	0.667	0.034%	0.072%	0.173%
Urinary Bladder	0.348	0.160%	0.828%	3.311%
	TOTAL:	**21.786%**	**36.190%**	**58.196%**

*PPV assumes a specificity of 99.5%

Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov). Prevalence database: "US Estimated Complete Prevalence Counts on 1/1/2018". National Cancer Institute, DCCPS, Surveillance Research Program, Data Modeling Branch, released April 2021, based on the November 2020 SEER data submission.

Klein EA, Richards D, Cohn A, et al. Clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation set. *Ann Oncol*. 2021;32(9):1167-1177.