GRAIL

MCD – Innovation for Population Health

FDA Medical Device Advisory Committee of the MCG Panel on Multi-Cancer Detection Devices

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We are not going to bend the cancer mortality curve by adding more single cancer screening tests

~70% DEATHS DUE TO CANCERS WITHOUT AVAILABLE SCREENING

Including Pancreas, Liver, Bladder, Brain, Esophageal, Kidney, Ovarian, Melanoma, Stomach, Endometrial, Oral, Larynx, Thyroid & Vulva

~30% DEATHS DUE TO CANCERS WITH AVAILABLE SCREENING*

MCD tests should be designed and evaluated differently from single cancer screening tests

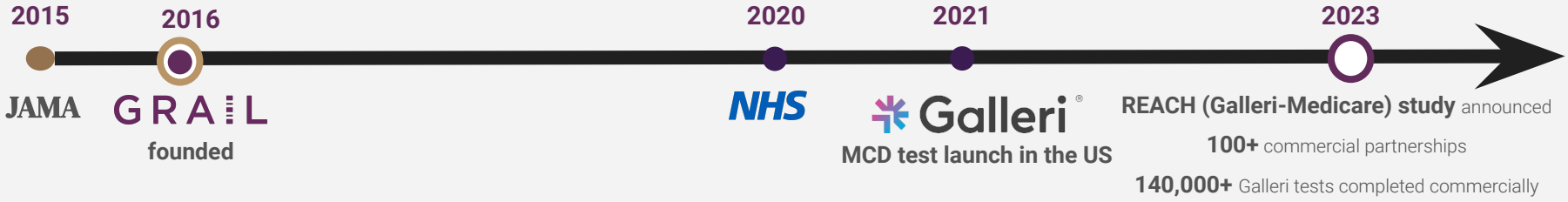
Designing an Optimal MCD Test

- **Shared cancer signal** that detects a broad range of deadly cancers
- High **specificity**
- **Signal origin** prediction is essential
- Does not contribute to **overdiagnosis** of indolent cancers
- **MCD tests complement** SOC screening and not replace it

Measuring Benefits of an MCD Test

- **Aggregate performance** of a test in the intended use population, not stratified to cancer types
- **PPV and cancer yield** are most important performance measures
- **Observed reduction in late stage cancer** incidence as an endpoint in clinical trials
- **Modeled mortality benefits**

Our rethinking is based on extensive experience, evidence generation and expert consultation



Annals of Oncology and *Cancer Cell 2020, 2021, 2023*

1 CCGA (n=15,254)

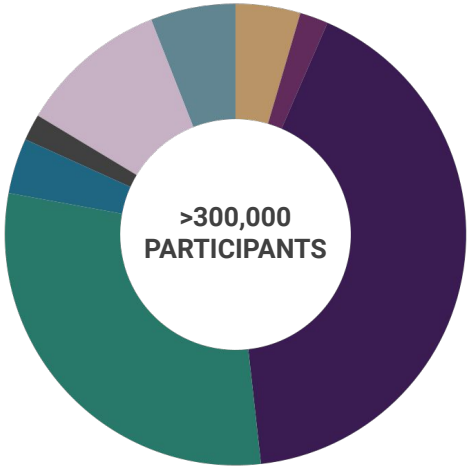
The Lancet 2023

2 PATHFINDER (n=6,662)

Lancet Oncology 2023

3 SYMPLIFY (n=6,242)

4 NHS-GALLERI (n≈142,321)



5 STRIVE (n=99,481)

6 SUMMIT (n=13,035)

7 REFLECTION (n≈17,000)

8 PATHFINDER 2 (n≈35,000)

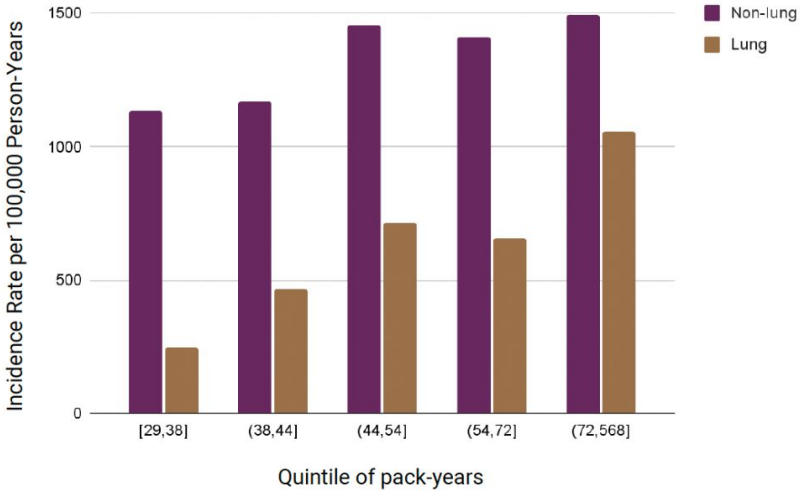
Aggregate measures are most important for MCD tests

Nearly five times as many cancer cases could be found by reporting any cancer versus a single cancer

Cancer Types Detected	Aggregate Sensitivity (%)	Aggregate Incidence (%)	Positive Predictive Value (%)	Total Cancers Detected per 100,000[c]
Lung	75	0.15	15	110
Any	45	1.16	44	506

- **PPV and cancer yield are maximized by detecting as many cancer types as possible (in aggregate)**
  - **There is an inverse relationship between aggregate sensitivity and cancer yield**

Risk of a non-lung cancer was higher than risk of lung cancer in NLST



Screening individuals for many cancers instead of only screening for individual cancers

For MCD tests, performance and clinical outcomes should be evaluated in **aggregate**, not by individual cancer type

Shared cancer signal with a **single low false positive rate** optimizes high specificity; highly accurate **signal origin prediction** is essential

PPV and cancer yield are the most important aggregate measures of the public health and clinical impact of an MCD test

Reduction in late stage cancer incidence and **cancer-specific mortality modeling** for MCD tests as we are doing in NHS-Galleri trial

Thank You