Cell-free DNA Fragmentation and Early Detection of Cancer

Victor Velculescu, M.D., Ph.D.

Achieving Excellence in Cancer Diagnosis

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Disclosure Information

Dr. Velculescu has the following financial relationships to disclose:

Founder of Personal Genome Diagnostics

Founder of Delfi Diagnostics

Scientific Advisory Board of Takeda, Genentech, Bristol-Myers Squibb, and Danaher
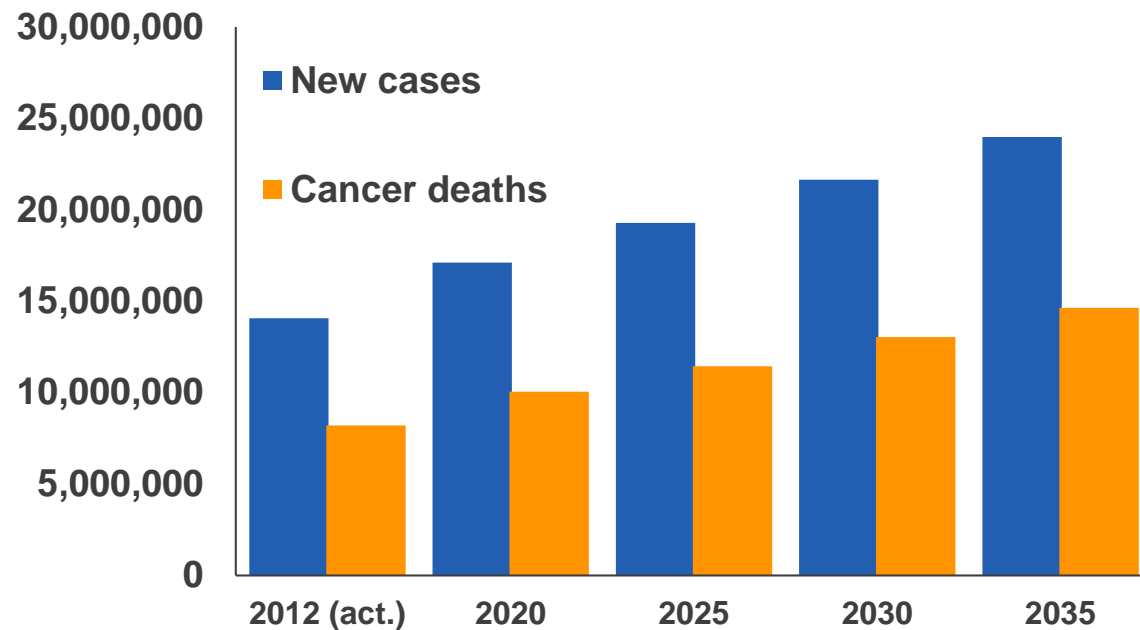
Some of the technology used in the study described in this presentation has been licensed and sublicensed to several entities, including Personal Genome Diagnostics, Delfi Diagnostics, Sysmex, Qiagen, Novartis, Ventana, Genzyme, Agios, LabCorp, Horizon Discovery and Esoterix. Under the terms of these license agreements, the University and Dr. Velculescu are entitled to fees and royalty distributions. These arrangements have been reviewed and approved by the Johns Hopkins University in accordance with its conflict of interest policies.

Non FDA Approved Use of Drugs or Products Referenced in this Presentation - NONE

- Victor Velculescu, MD, Ph.D.

Cancer is a major cause of death due to late detection

14 million diagnosed and 8 million die from cancer each year

World Cancer Projections

- New cases
- Cancer deaths

	2012 (act.)	2020	2025	2030	2035

Source: Globocan, http://globocan.iarc.fr

Cancer Diagnosis at Advanced Stages

- ovarian
- colon
- lung
- breast

0   20   40   60

Source: NCI, https://progressreport.cancer.gov
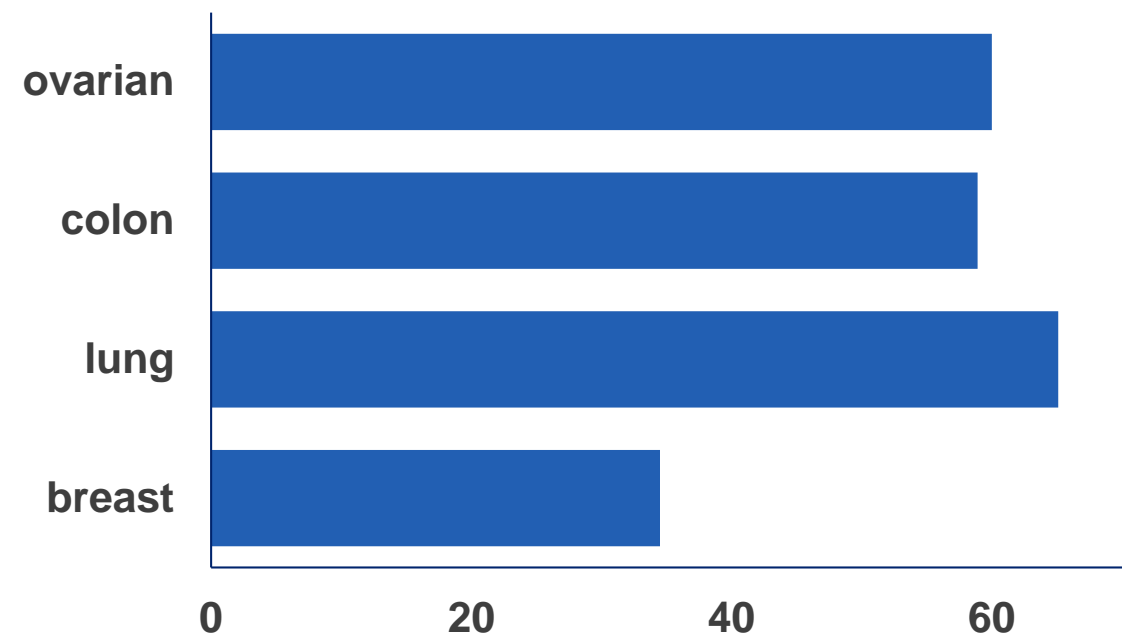
Early detection saves lives and is cost effective

Early detection can save 4-6 million lives per year
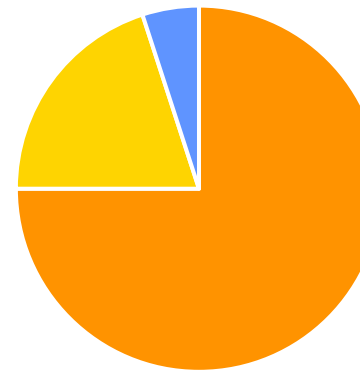
RELATIVE 5 YEAR CANCER SURVIVAL RATES		
Cancer Type	Late Detection	Early Detection
Breast	27%	99%
Colorectal	14%	90%
Lung	5%	56%
Ovary	29%	92%
Stomach	5%	68%

Economic savings of early detection could be $100-1,000 Bn
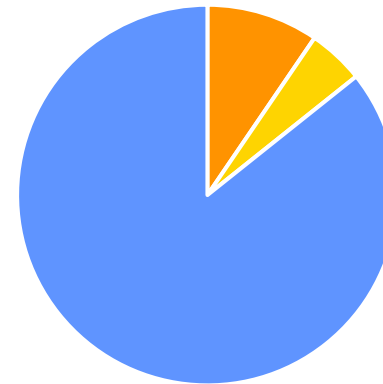
Cost

Lives saved

- Cancer therapy
- Detection of recurrence
- Early detection

Mariotto et al, 2011; Bradely et al, 2008;
Yabroff et al, 2011; Blumen et al, 2016; WHO, 2014.
G. Meijer et al., unpublished.

Liquid biopsy approaches for sensitive and specific detection of cancer

Tumor DNA entering circulation

Cell free DNA isolated from plasma

Paired-end massively parallel sequencing

Copy number analysis (Digital Karyotyping)

Rearrangement analysis (PARE)

Targeted error correction sequencing (TEC-Seq)

Fragmentation profiles (DELFI)

Normal

Sequence Alteration

Fragmentation Profiles

Translocation

Amplification

Deletion

Chromosome Arm Loss

Chromosome Arm Gain

Detection of tumor-specific alterations

Leary, *Science TM*, 2010
Leary, *Science TM*, 2012
Phallen, *Science TM*, 2017
Cristiano, *Nature*, 2019

Genome–wide cell–free DNA fragmentation in patients with cancer

Stephen Cristiano[1,2,15], Alessandro Leal[1,15], Jillian Phallen[1,15], Jacob Fiksel[1,2,15], Vilmos Adleff[1], Daniel C. Bruhm[1], Sarah Østrup Jensen[3], Jamie E. Medina[1], Carolyn Hruban[1], James R. White[1], Doreen N. Palsgrove[1], Noushin Niknafs[1], Valsamo Anagnostou[1], Patrick Forde[1], Jarushka Naidoo[1], Kristen Marrone[1], Julie Brahmer[1], Brian D. Woodward[4], Hatim Husain[4], Karlijn L. van Rooijen[5], Mai-Britt Worm Ørntoft[3], Anders Husted Madsen[6], Cornelis J. H. van de Velde[7], Marcel Verheij[8], Annemieke Cats[9], Cornelis J. A. Punt[10], Geraldine R. Vink[5], Nicole C. T. van Grieken[11], Miriam Koopman[5], Remond J. A. Fijneman[12], Julia S. Johansen[13], Hans Jørgen Nielsen[14], Gerrit A. Meijer[12], Claus Lindbjerg Andersen[3], Robert B. Scharpf[1,2]* & Victor E. Velculescu[1]*

DNA evaluation of fragments for early interception (DELFI)

Highly collaborative and interdisciplinary effort involving cancer genomics, biostatistics, computational biology, oncology, pathology from JHU School of Medicine and School of Public Health as well as national and international collaborators
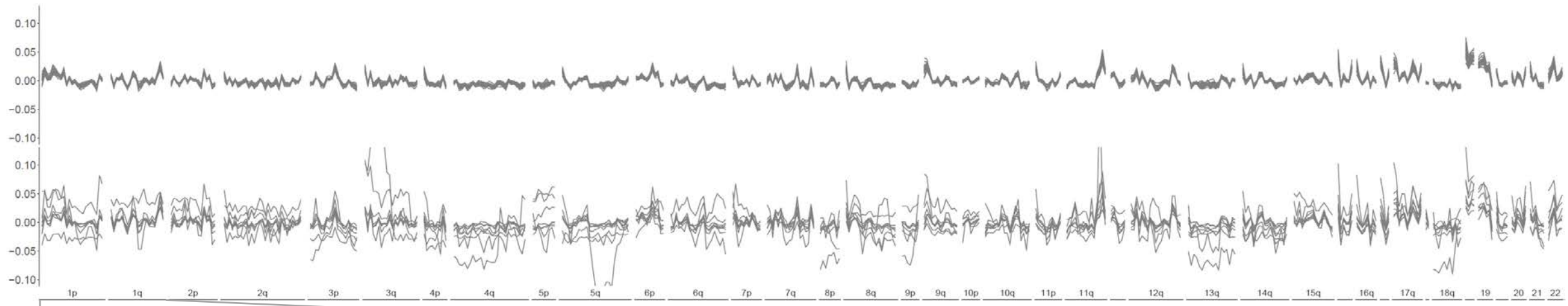
DELFI approach for detection of ctDNA

Noninvasive cancer screening (DELFI)

White blood-cell derived cfDNA

Tumor-derived cfDNA

Genome position

Machine learning

Cancer

Healthy

Biliary Breast Colon Gastric Lung Ovary Pancreas
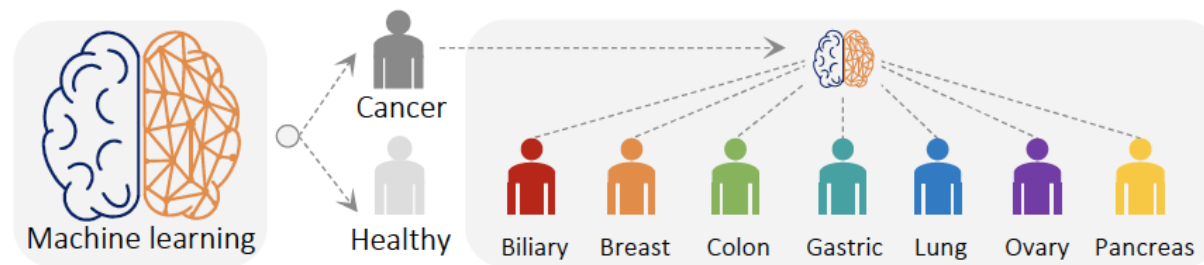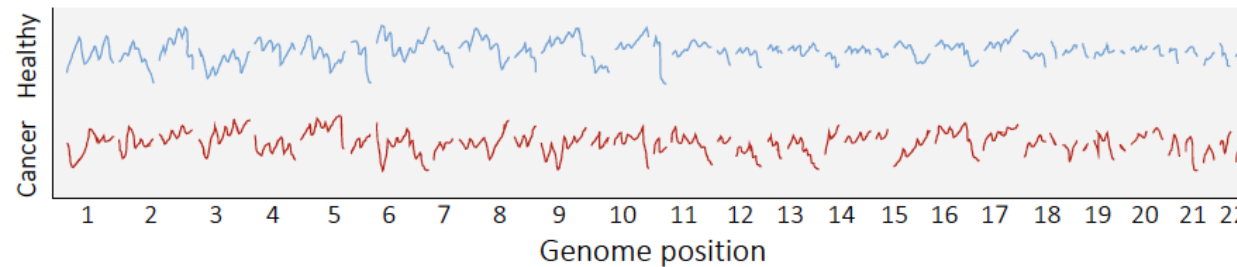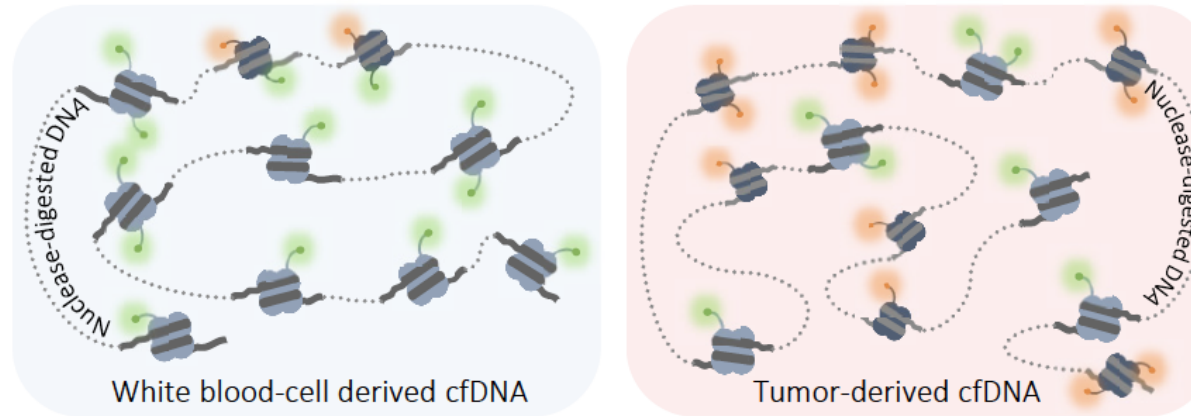
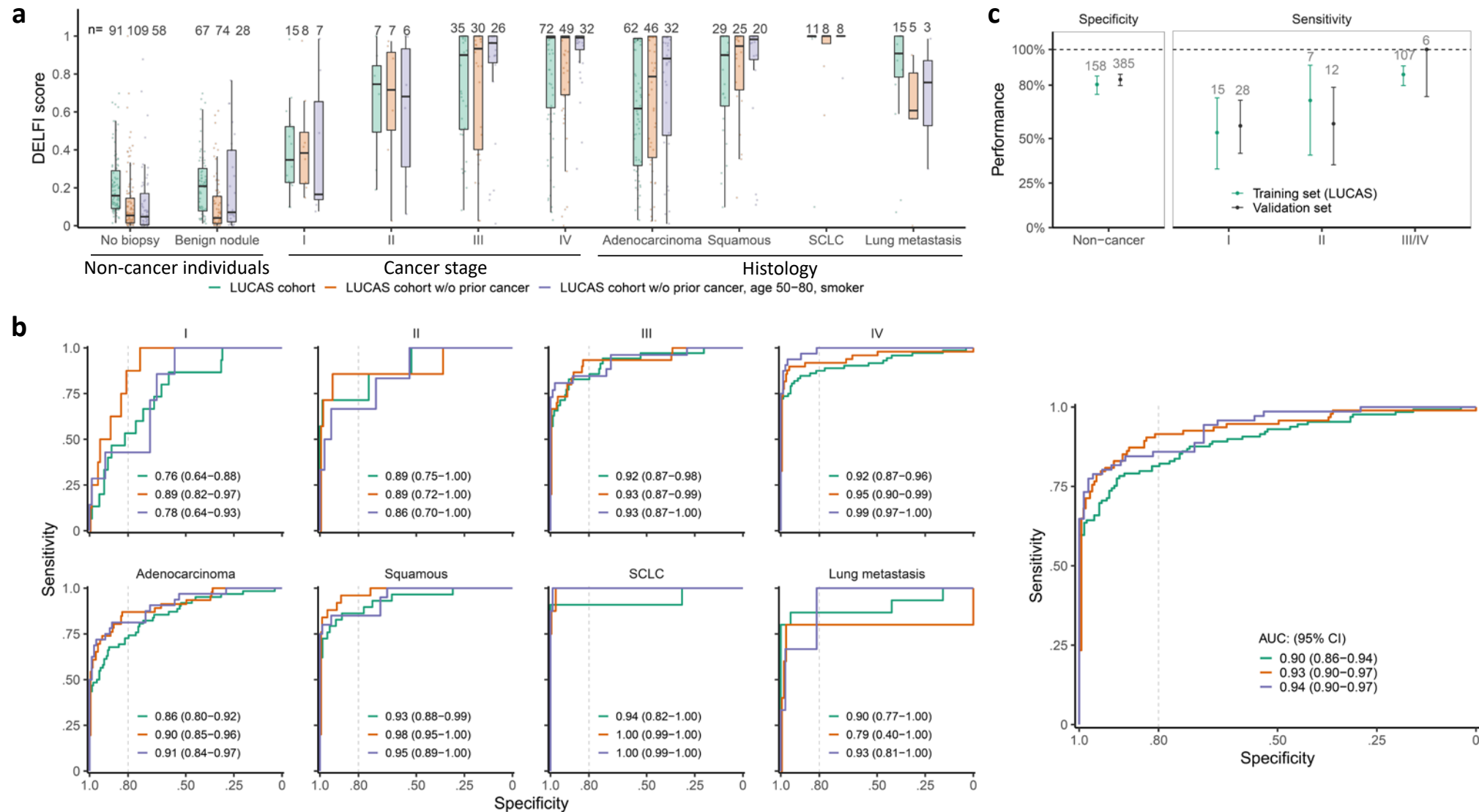Cristiano, Leal, Phallen, Fiksel, Scharpf et al., *Nature*, 2019

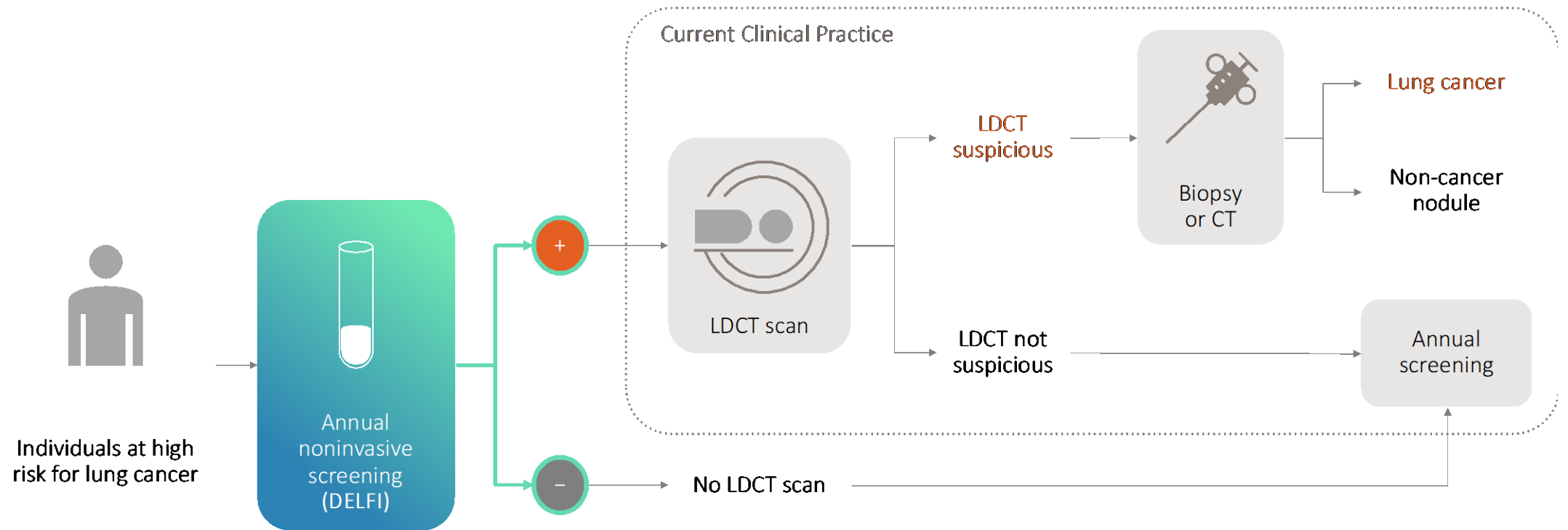# cfDNA fragmentation profiles are altered in patients with cancer

DELFI is highly sensitive and specific for cancer detection

Cancer type	Individuals analyzed	Sensitivity 95% specificity	98% specificity
Lung	12	100%	100%
Ovarian	28	89%	89%
Bile duct	26	88%	81%
Gastric	27	81%	81%
Colorectal	27	81%	80%
Pancreatic	34	71%	65%
Breast	54	70%	57%
Healthy	215	<5%	<2%

Cristiano, Leal, Phallen, Fiksel, Scharpf et al., *Nature*, 2019

DELFI has high sensitivity and specificity
for detection of lung cancer

Mathios, Johansen, Cristiano, Medina, Phallen et al., *Nature Communications, 2021*

DELFI as a pre-screening tool for lung cancer detection

Mathios, Johansen, Cristiano, Medina, Phallen et al., *Nature Communications, 2021*

Fragmentation profiles are different among cancer types
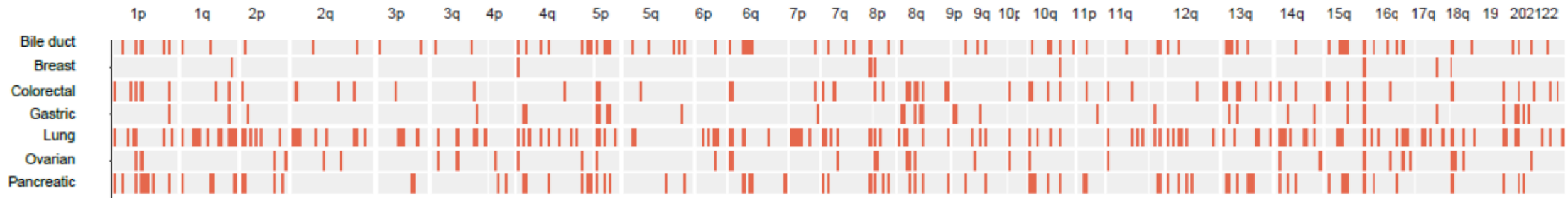
and can be used to identify the tissue of origin

DELFI can identify the tissue of origin of cancer

Tumor Type	Patients detected	Top Prediction	Top Two Predictions
Breast	42	76%	91%
Colorectal	24	71%	79%
Gastric	24	67%	79%
Lung	30	53%	77%
Pancreatic	24	50%	67%
Ovarian	27	48%	59%
Bile duct	23	44%	65%
Total	**194**	**61%**	**75%**

Conclusions and Opportunities

- Majority of cancers are detected at advanced stages when response to therapy and survival is poor

- Early cancer detection could reduce morbidity and mortality

- Current liquid biopsy approaches have limitations for early detection due to limited observations and WBC variants in healthy individuals

- Genome-wide cfDNA fragmentation profiles reflect abnormal packaging and genomic content of cancer genomes

- Fragmentation profiles detect high fraction early stage cancers and provides new avenue for early cancer detection and intervention

- Clinical trials for lung and other cancers underway (NCT04825834)

Acknowledgements