THE FUTURE OF CANCER DATA: UNLOCKING INSIGHTS WITH PATHOLOGY REPORTING



Unlocking the Value of Molecular Profiling: The Power of the Integrated Pathology Matthew Oberley, MD, PhD OCTOBER 6 | 3:45-4:15 PM CT



COLLEGE of AMERICAN PATHOLOGISTS Laboratory Quality Solutions

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Unlocking the Value of Molecular Profiling: The Power of the Integrated Pathology Report

Matthew Oberley, MD, PhD

October 6, 2023



Disclaimer

- Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all available information concerning the patient's condition, the FDA prescribing information for any therapeutic, and in accordance with the applicable standard of care. Whether or not a particular patient will benefit from a selected therapy is based on many factors and can vary significantly.
- The materials may discuss uses and dosages for therapeutic products that may or may not have not been approved by the United States Food and Drug Administration. A qualified healthcare professional should be consulted before using any therapeutic product discussed.
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From Scalpels to Genomes

The Changing Landscape of Cancer Care

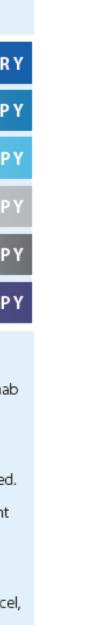


Oncology is Evolving at an Unprecedented Rate

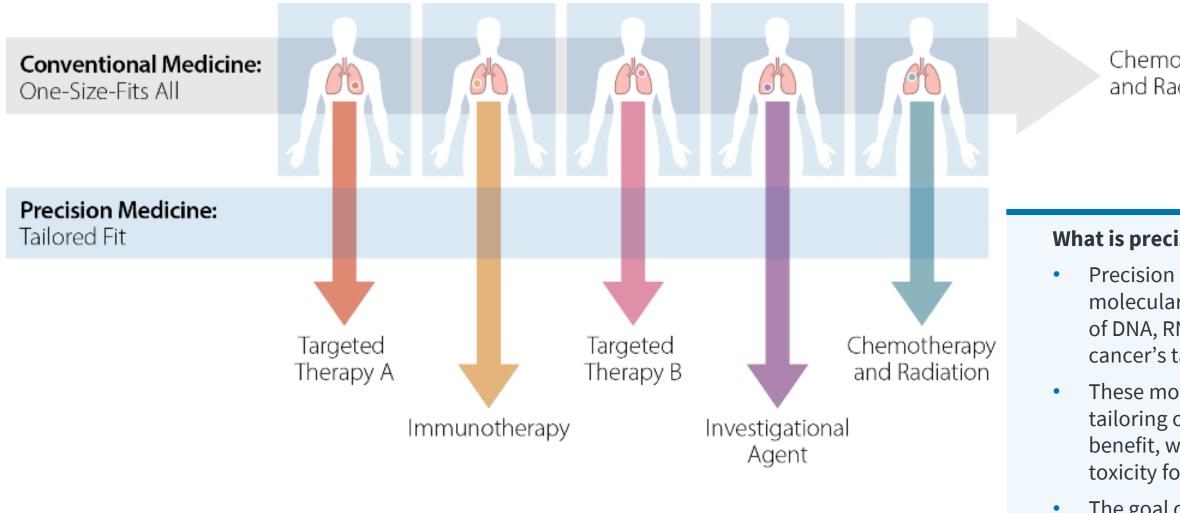
Milestones in Cancer Therapy (1900–2023)

1900-1924	1925-1949	1950-1974	1975-1999	2000-2023
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 1902 – Boveri suggests cancer arises from chromosomally damaged, rapidly dividing single cells. 1909 – Ehrlich proposes the immune system normally suppresses tumor formation. 1911 – Rous shows cancers can be caused by viruses. 	 1941 – Huggins shows that hormone therapy can cause prostate tumors to regress. 1942 – Nitrogen mustard used as the first chemotherapeutic agent to treat cancer. 1949 - FDA approves nitrogen mustard for cancer. 	 1950s - Other alkylating agents and antimetabolites are adopted as therapies. 1958 - Combination chemotherapy shown to improve outcomes. 1972 - Tamoxifen approved in UK and Europe. 	 1977 – FDA approves tamoxifen, the first hormone therapy drug. 1979 - TP53 discovered. 1984 - Her2 (neu) identified. 1994/5 - BRCA1/2 cloned. 1998 – FDA approves the first biomarker-targeted therapy, trastuzumab. 	 2000 – FDA approves first antibody-drug conjugate, gemtuzumab ozogamicin. 2004 – First anti- angiogenesis agent, bevacizumab, approved. 2011 – First checkpoint inhibitor, ipilimumab, approved. 2017 – First CART-cell therapy, tisagenlecleucel, approved.





Precision Oncology Tailors Treatment to Each Patient





Chemotherapy and Radiation

What is precision oncology?

Precision oncology is the use of molecular profiling – including analysis of DNA, RNA, and protein - to identify a cancer's targetable alterations.

These molecular insights enable the tailoring of therapy to patients likely to benefit, while sparing exposure and toxicity for those who will not.

The goal of precision oncology is to deliver the right therapy to the right patient at the right dose and time.

Biomarkers Guide the Way to Targeted Therapies

Predictive **Biomarkers**

Identify patients who will have a favorable (or unfavorable) response to an intervention.

Diagnostic **Biomarkers**

Indicate presence of cancer or give information on cancer type, stage, or progression.

NSCLC patients with EGFR activating mutations have longer progression-free survival than EGFR wildtype patients when treated with erlotinib. EGFR mutational status is. therefore, a predictive biomarker for erlotinib response.

The presence of specific KRAS mutations in tumor or stool DNA is a diagnostic biomarker for colorectal cancer. Mutated KRAS can also act as a predictive and prognostic biomarker in this cancer.

Prognostic **Biomarkers**

Provide information on the likely outcome or trajectory of a patient's cancer (e.g., survival, recurrence, progression).

> HER2 overexpression is associated with more aggressive tumors and poorer outcomes in breast cancer.² Identification of HER2 as prognostic biomarker led to targeted therapies, such as trastuzumab, that inhibit the HER2 pathway and significantly improve outcomes for HER2positive patients. 3*

1. Brugger W, et al. (2011) J Clin Oncol. 2. Slamon DJ, et al. (1987) Science. 3. Slamon DJ, et al. (2001) N Engl J Med.

A molecular target acted upon by the associated drug.

KRASGIDC is a biomarker and target for sotorasib (AMG 510) in non-small cell lung cancer (NSCLC).

A phenotype that is more likely to respond to the associated drug.

High tumor mutational burden (TMB) is a biomarker for response to immune checkpoint inhibitors.

A component of a pathway complementary to that of the target.

Mutations in homologous recombination DNA repair pathway genes, such as BRCA1, are biomarkers for response to PARP inhibitors.

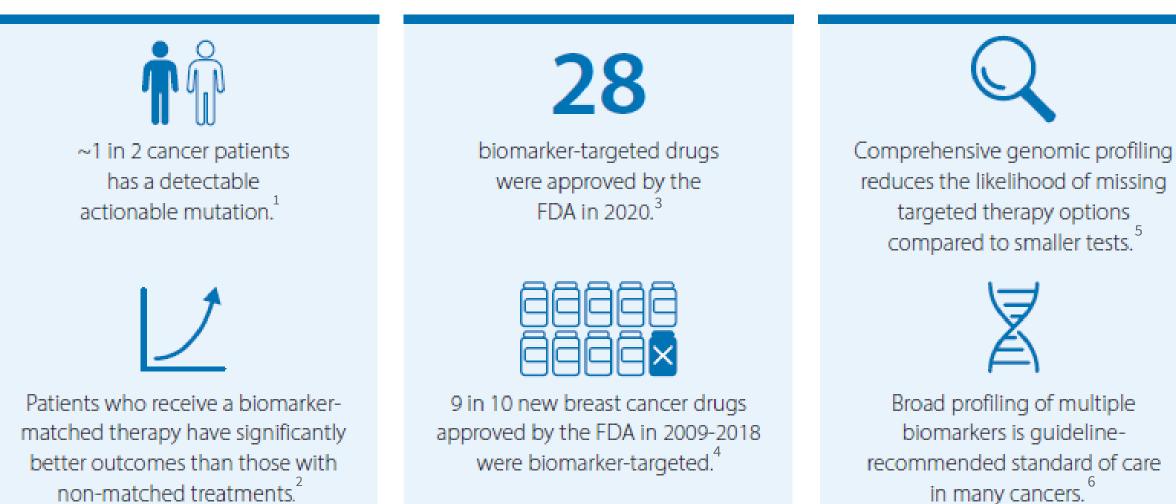


DIRECT BIOMARKER

INDIRECT BIOMARKER

PATHWAY BIOMARKER

Biomarker Testing and Matched Therapies Improve Outcomes



- 1. Nono Djotsa A, et al. (2023) Journal of Clin Oncol.
- 2. Tsimberidou AM, et al. (2012) Clin Cancer Res.
- 3. Chakravarty D, et al. (2022) Journal of Clin Oncol.
- 4. Leo CP, et al. (2020) Nat Rev Drug Discov.
- 5. Paz-Ares L, et al. (2022) Lung Cancer.
- Palmero R, et al. (2021) JCO Prec Oncol. 6.







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Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion

ASCO

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 \mathcal{O} Debyani Chakravarty, PhD¹; Amber Johnson, PhD²; Jeffrey Sklar, MD, PhD³; Neal I. Lindeman, MD⁴; Kathleen Moore, MD⁵; Shridar Ganesan, MD, PhD⁶; Christine M. Lovly, MD, PhD⁷; Jane Perlmutter, PhD⁸; Stacy W. Gray, MA, MD⁹; Jimmy Hwang, MD¹⁰; Christopher Lieu, MD¹¹; Fabrice André, MD, PhD¹²; Nilofer Azad, MD¹³; Mitesh Borad, MD¹⁴; Laura Tafe, MD¹⁵; Hans Messersmith, MPH¹⁶; Mark Robson, MD¹; and Funda Meric-Bernstam, MD²

"Patients with metastatic or advanced cancer should undergo genomic sequencing in a certified laboratory if the presence of one or more specific genomic alterations has regulatory approval as biomarkers to guide the use of or exclusion from certain treatments for their disease. Multigene panel–based assays should be used if more than one biomarker-linked therapy is approved for the patient's disease. Site-agnostic approvals for any cancer with a high tumor mutation burden, mismatch repair deficiency, or neurotrophic tyrosine receptor kinase (NTRK) fusions provide a rationale for genomic testing for all solid tumors."

Chakravarty et al., JCO. (2022) Available as open-access at: https://ascopubs.org/doi/full/10.1200/JCO.21.02767



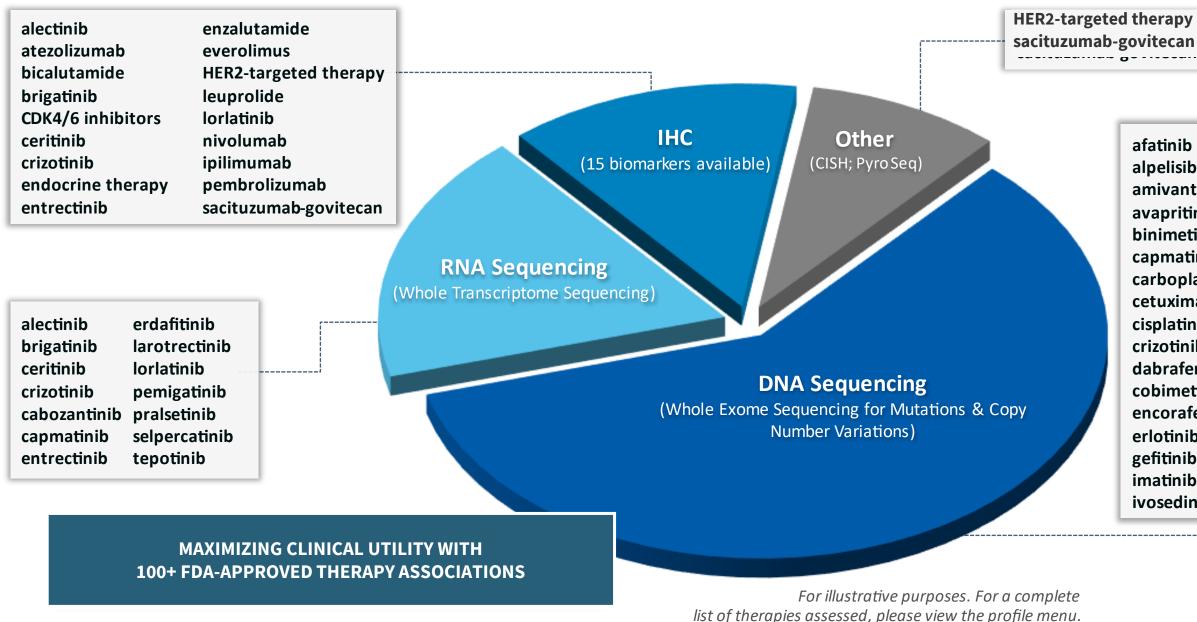


Comprehensive Molecular Profiling

Providing Value Across the Patient Journey



Adherence to Guidelines Requires a Multi-Technology Approach





HER2-targeted therapy temozolomide

afatinib alpelisib amivantamab avapritinib binimetinib capmatinib carboplatin cetuximab cisplatin crizotinib dabrafenib cobimetinib encorafenib erlotinib gefitinib imatinib ivosedinib

mobocertinib niraparib imatinib olaparib osimertinib oxaliplatin panitumumab pembrolizumab regorafenib rucaparib sotorasib sunitinib T-DM1 temozolomide trametinib vemurafenib

Comprehensive Molecular Profiling (CMP): The Most In-depth Insights into a Patient's Cancer

What is CMP?

Comprehensive molecular profiling (CMP) analyzes DNA (by whole exome sequencing), RNA (by whole transcriptome sequencing), and protein (using immunohistochemistry) to generate the most in-depth picture of a patient's cancer.

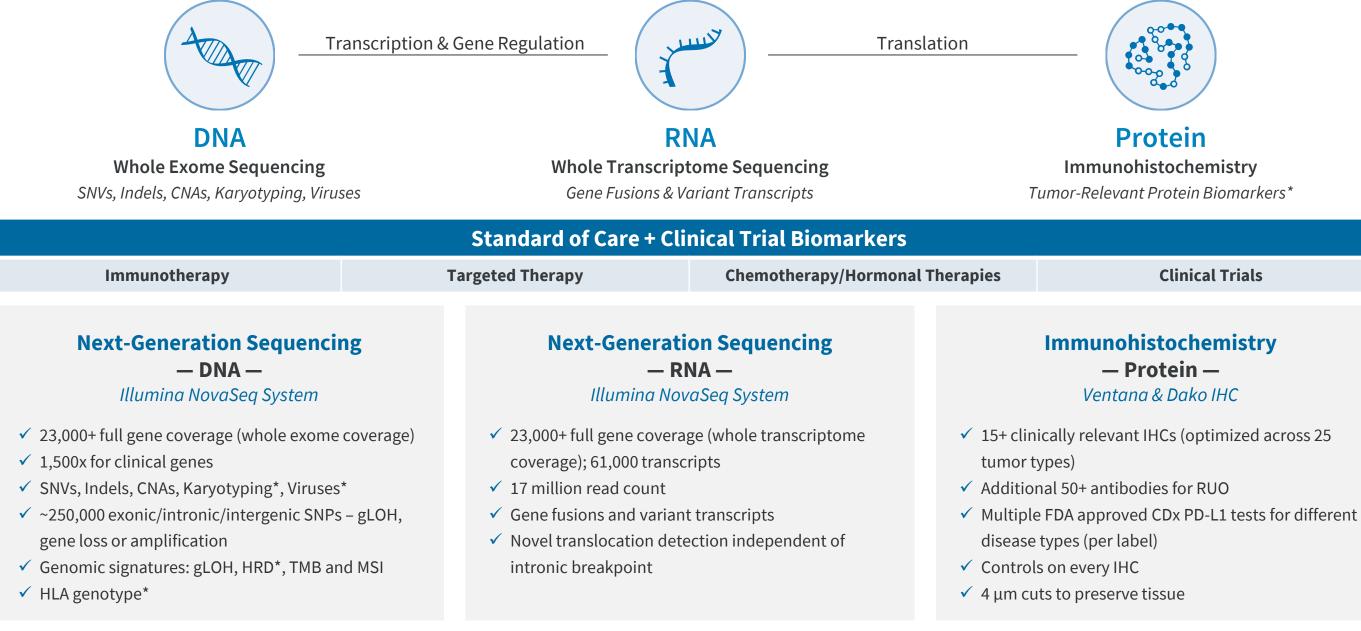
- CMP is standard of care for advanced stage cancer to **predict** the most appropriate therapy.
- Molecular testing is also an integral part of the **diagnostic** workup of many cancer types.
- As molecular profiling becomes more comprehensive, there is increasing **overlap** between predictive and diagnostic testing.



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Best-in-Class Profiling Reveals a More Comprehensive Molecular Blueprint

Analyzing DNA, RNA, and proteins to reveal a more complete molecular blueprint to guide precise and individualized treatment decisions.



*Certain tests or features are not available in all locations. See website for details.



Clinical Trials

The Power of DNA and RNA Across 23,000+ Genes, Proteins + AI







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Caris Company Footprint

4 PRECISION MEDICINE FACILITIES

(Phoenix and Dallas) Totaling 360K+ Sq. Ft.



Blood / Solid Clinical Lab (Dallas, TX) Clinical Tissue and Blood Lab 138K sq. ft. (under construction)



Blood Lab (Phoenix, AZ) Clinical Blood Lab 35K sq. ft.

Clinical Lab (Phoenix, AZ) Clinical Tissue Lab 130K sq. ft.



R&D Lab (Phoenix, AZ) Drug Target Discovery Lab 59K sq. ft.



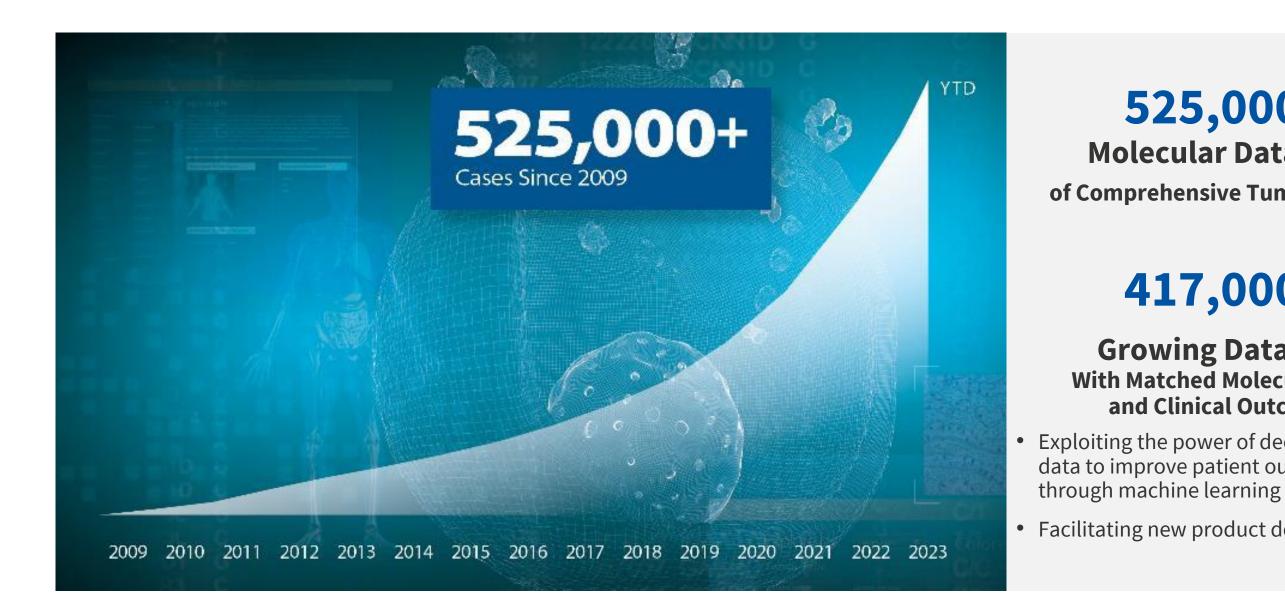


FOOTPRINT OF 50 NOVASEQS



Over 1 trillion "reads" every day Enhanced depth of coverage in NGS DNA

Pioneer in Molecular Science – Robust Data to Inform Precision Medicine







525,000+ **Molecular Database** of Comprehensive Tumor Profiles

417,000+

Growing Database With Matched Molecular Data and Clinical Outcomes

• Exploiting the power of deep molecular data to improve patient outcomes

• Facilitating new product development



Synoptic Reporting

Streamlining the Collection of Biomarker Data for Optimal Patient Care

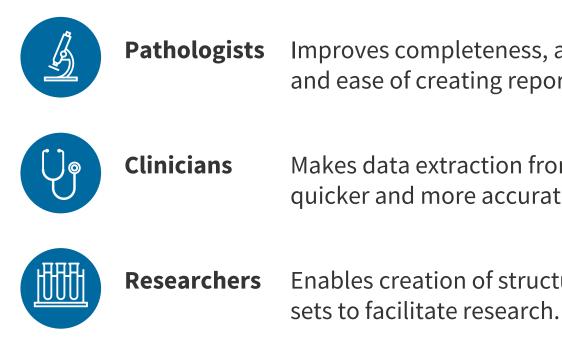


Synoptic Reporting is Vital in Precision Oncology

What is synoptic reporting?

- Synoptic reporting is the systematic and structured • recording of patient medical information.
- Instead of freeform text, synoptic reporting employs • predefined templates or checklists with specific fields.
- The aim is to improve care by ensuring consistency, ٠ accuracy, and completeness in medical records.
- In oncology, synoptic reporting is used to standardize ٠ reporting of diagnoses, pathology, and surgeries.
- Synoptic reporting ensures each patient gets the appropriate workup, with all relevant data in one place.

Benefits of Synoptic Reporting





Improves completeness, accuracy, and ease of creating reports.

Makes data extraction from reports quicker and more accurate.

Enables creation of structured data

CAP is at the Forefront of Structured Data Capture

- CAP develops cancer biomarker synoptic reports to capture structured data for inclusion in surgical pathology reports.
- There are currently >100 CAP Cancer Biopsy, Resection and Biomarker Protocols and electronic Cancer Protocols (eCP).

CAP Cancer Protocols are a resource developed by pathologists for pathologists to help deliver the synoptic information necessary for quality patient care and data aggregation.



Based on timely data from standard-setting organizations:

AJCC (8th edition/9th CAP/ASCO Center WHO Blue Books FIGO Guidelines version chapters)

CAP Cancer Protocols

- Incorporate latest standards to help pathologists and labs keep up with reporting advances and updates.
- Provide guidelines for collecting essential data elements for complete reporting and optimal patient care.
- Allow directed flow of biomarker data from the reference testing lab in a concise, beneficial manner for the pathologist, oncologist, and patient.
- Offer explanatory notes, references, and case summaries with standard question and answer sets.

CAP Electronic Cancer Protocols (eCP)

 Provide core data elements mandated for accreditation by ACoS-CoC & CAP LAP.

CAP Biomarker Reporting Protocols

- Currently cover 10 organ systems and 150+ biomarkers.
- Available in electronic and paper formats.

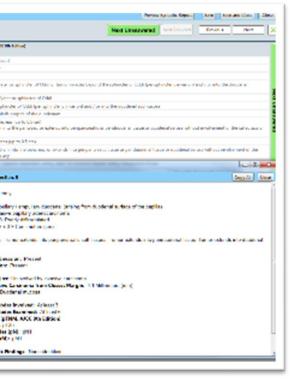


Process Overview: Paper Protocol to eCP

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CAP Biomarker Templates Provide Guidance on Testing



Template for Reporting Results of Biomarker Testing of Specimens From Patients With Non-Small Cell Carcinoma of the Lung

Version: 2.0.1.0 Protocol Posting Date: November 2021 This biomarker template is not required for accreditation purposes but may be used to facilitate compliance with CAP Accreditation Program Requirements

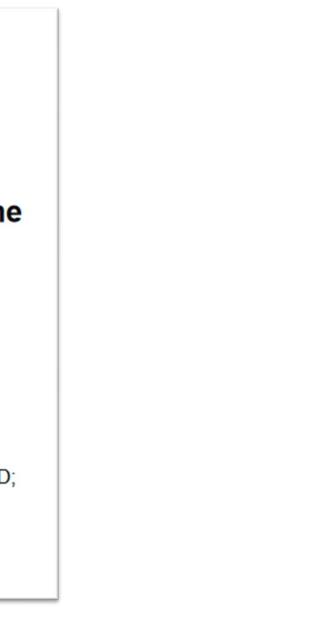
Authors

Brett W. Baskovich, MD*; Frank Schneider, MD; Alexander Baras, MD, PhD; George G. Birdsong, MD; Patrick L. Fitzgibbons, MD, FCAP; Joseph D. Khoury, MD; Raja R. Seethala, MD.

With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees. * Denotes primary author.







CAP Biomarker Reporting Template: Lung

CAP Approved	Lung.Bmk_2.0.1.0.REL_CAPCP	- Select Metadata Items
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Where Does Biomarker Testing Data Come From?

Most cancer biomarker testing is carried out at third party reference laboratories.

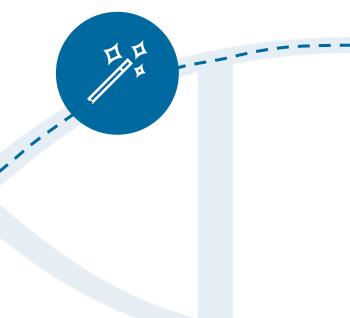
> PDF reports require **further** manipulation to get data into a synoptic report for pathologist sign-off and oncologist use.

Results are typically provided to the clinical laboratory in **PDF format.**

These manipulations are **usually manual**, and thus unscalable, error-prone, and time-consuming, plus often not remunerated.



Auto-population would help reduce the need for direct data entry and opportunities for errors.



Biomarker Testing is Growing Rapidly

Dramatic recent increases in:

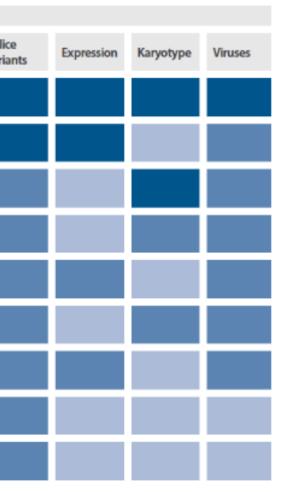
- Utilization of biomarker testing.
- Comprehensiveness of profiling.
- **Overlap** between diagnostic and predictive biomarker profiling.

Potential to help pathologists gather all relevant data to inform patient care.

However, to take full advantage there must be **more efficient transfer** of biomarker data into reports.

	Number of	Molecules Detected	Molecular Alterations or Features			
Assay Type	coding genes analyzed		Base Changes	InDels, CNVs	Fusions	Spli vari
СМР	~20,000	DNA, RNA, Protein				
WTS	~20,000	RNA				
WES or WGS	~20,000	DNA				
CGP	100s-1000s	DNA				
Cur		RNA				
Multigene	Hotspot Large: 50-	DNA				
Panel		RNA				
Single Gene	One	DNA				
Testing		RNA				
Typical	lly tested	Sometimes	tested	Not typ	ically tested	





How Can We Improve Transfer of Biomarker Data into Reports?



Rapid growth in biomarker testing demands a scalable, efficient, and accurate data transfer solution.



Mapping logic would be required for seamless electronic auto-population of reference lab results into a structured data capture format.

This auto-population would **support** timely diagnosis, enhance patient care, and reduce pathologist data entry.

SPECIAL SERIES: CANCER CLASSIFICATION SYSTEMS **College of American Pathologists Cancer Protocols: From Optimizing Cancer Patient Care** to Facilitating Interoperable Reporting and **Downstream Data Use**

Vanda F. Torous, MD²: Ross W. Simpson, MD²: Jyoti P. Balani, MD²: Alexander S. Baras, MD, PhD⁴: Michael A. Berman, MD⁴: George G. Birdsong, MD*; Giovanna A. Giannico, MD*; Gladell P. Paner, MD*; Jason R. Pettus, MD*; Zack Sessions, PharmD**; S. Joseph Sirintrapun, MD11; John R. Srigley, MD12; and Samantha Spencer, MD10

- The College of American Pathologists Cancer Protocols have offered guidance to pathologists for standard
- cancer pathology reporting for more than 35 years. The adoption of computer readable versions of these
- capture and reporting to downstream consumers of these data such as the cancer surveillance community. This
- paper reviews the history of the Cancer Protocols and electronic Cancer Checklists, outlines the current use of these critically important cancer case reporting tools, and examines future directions, including plans to help improve the integration of the Cancer Protocols into clinical, public health, research, and other workflows.

JCD Clin Cancer Inform 5:47-55. © 2021 by American Society of Clinical Oncology

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protocols by electronic health record and laboratory information system (LIS) vendors has provided a mechanism for pathologists to report within their LIS workflow, in addition to enabling standardized structured data

Initiative to Directly Integrate Molecular Results

Objective

Assess how CAP eCPs can provide a targeted evidence-based framework for direct mapping of molecular biomarker data from reference labs into corresponding CAP cancer biomarker synoptic report data elements.

Method

- Biomarker testing
 - Caris' comprehensive profiling provides maximum insights in one test, including diagnostic and predictive biomarkers, thereby reducing duplicative testing.

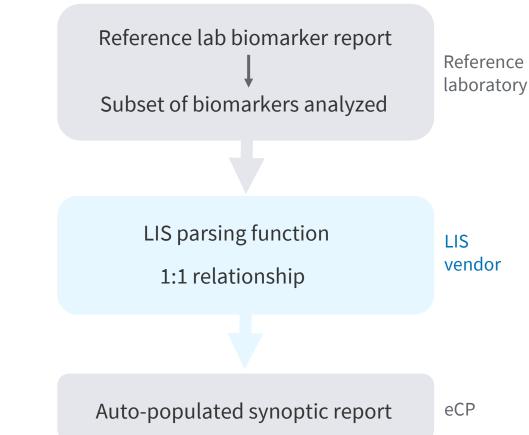
• Data processing

- Each data element within a CAP cancer biomarker template has an assigned unique identifier (Ckey).
- Ckeys can be leveraged by reference labs to direct the mapping of results into a CAP eCP residing on an institution's LIS/EHR server.
- This direct result-to-protocol transfer solution would be available to all reference labs/EHR/LIS vendors.

Proof of Concept

The current development work with Caris and mTuitive is a first step in proof of concept.

Conceptual Workflow





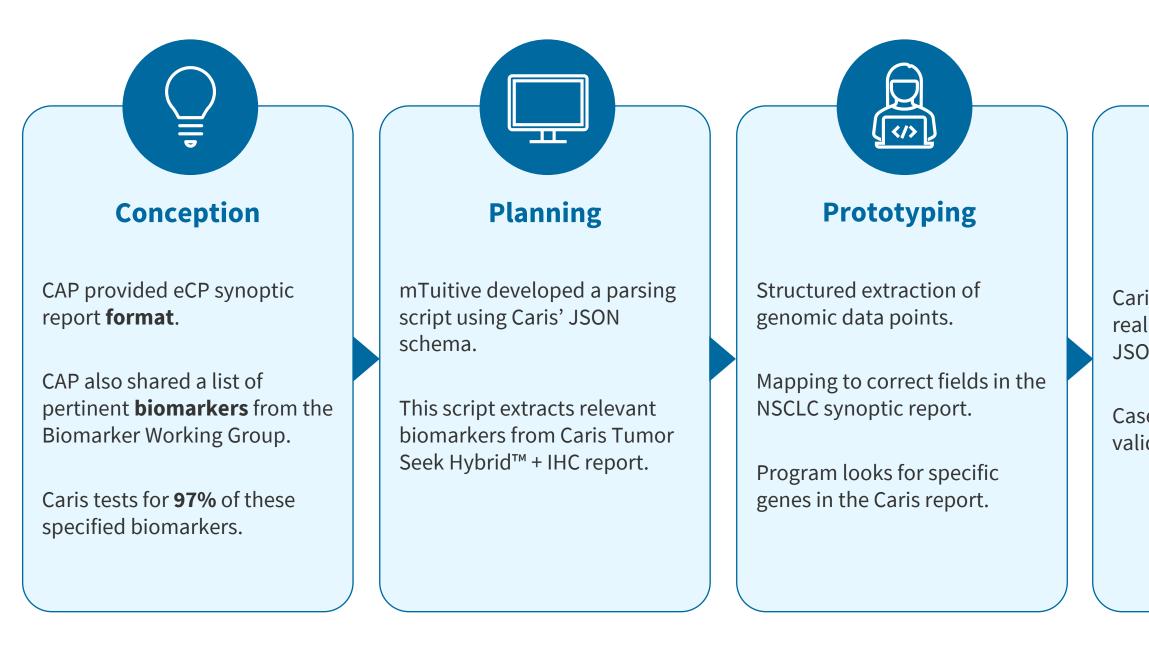


Developing a Data Transfer Solution for Auto-population of CAP Synoptic Reports

A Collaboration of CAP with Caris Life Sciences and mTuitive Inc.



Developing a Synoptic Report Auto-population Solution





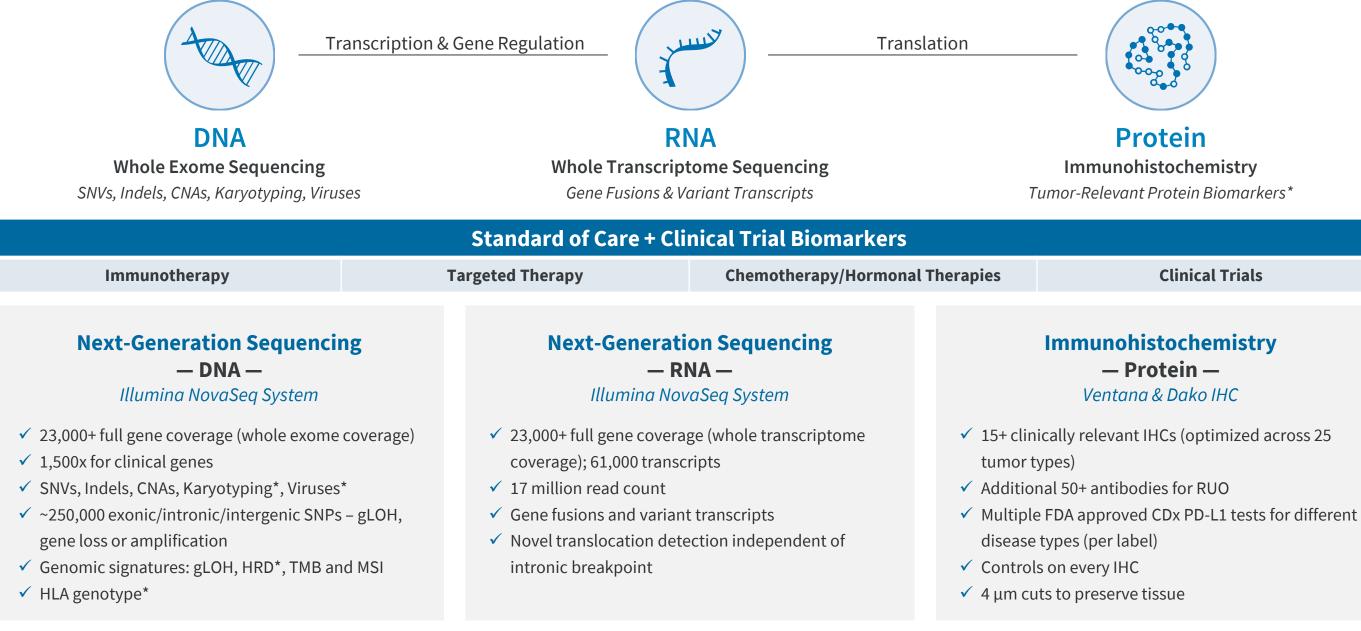


Caris provided 25 deidentified real-world NSCLC cases in JSON format.

Cases run through process to validate parsing and mapping.

Best-in-Class Profiling Reveals a More Comprehensive Molecular Blueprint

Analyzing DNA, RNA, and proteins to reveal a more complete molecular blueprint to guide precise and individualized treatment decisions.

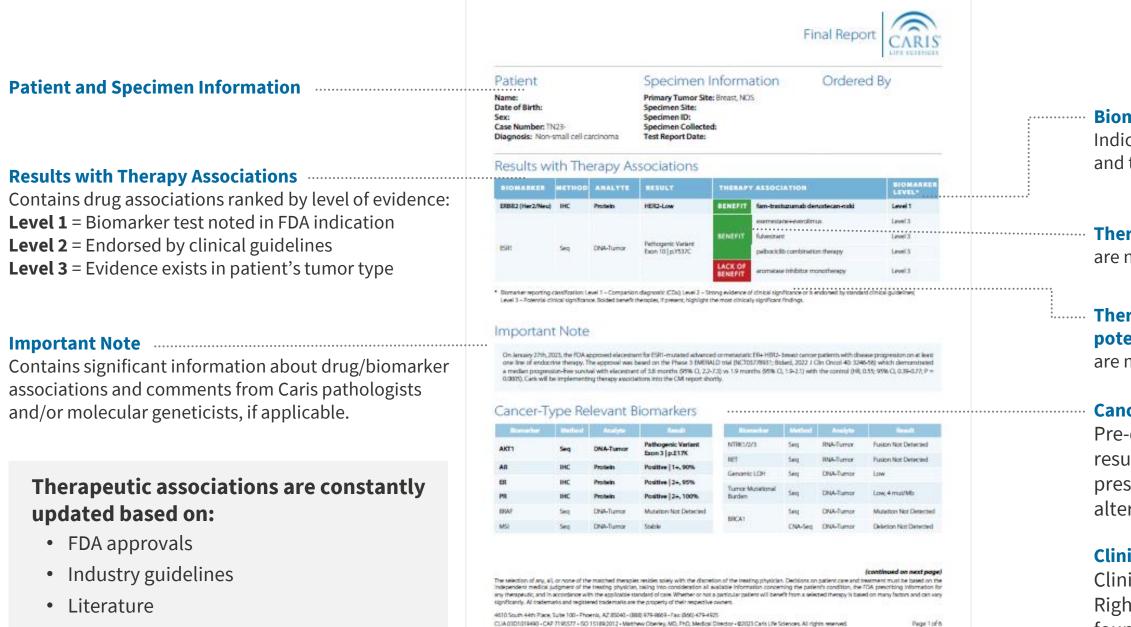


*Certain tests or features are not available in all locations. See website for details.



Clinical Trials

Easy-to-Interpret Results – Caris Report



• Physician feedback



Biomarker Levels

Indicates the strength of evidence and testing (e.g., Level 1 is a FDA CDx).

Therapies with potential Benefit are noted in **green**.

Therapies with potential Lack of Benefit are noted in red.

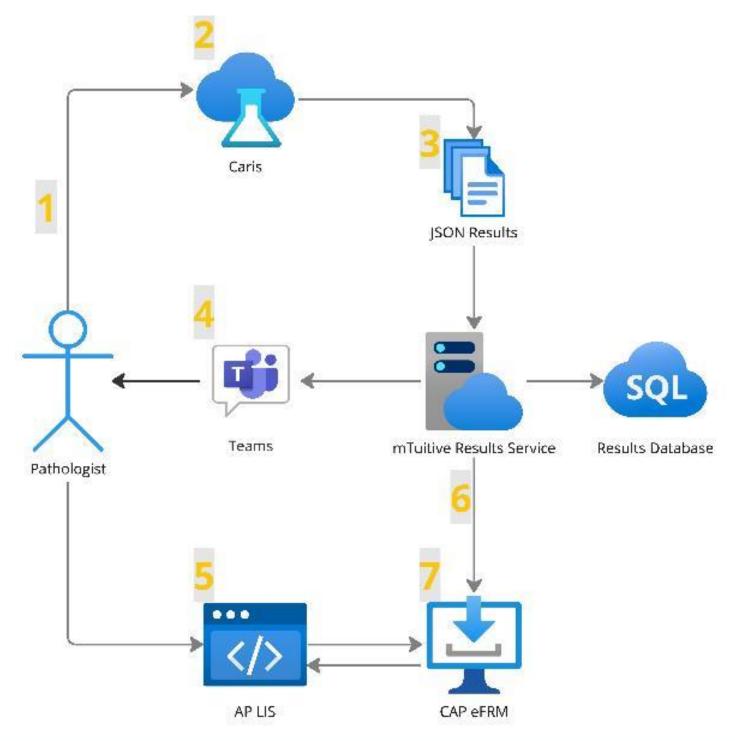
Cancer-Type Relevant Biomarkers

Pre-defined biomarkers whose results will show regardless of presence or absence of an alteration.

Clinical Trials

Clinical trial information, including Right-In-Time Clinical Trials, can be found later in the report.

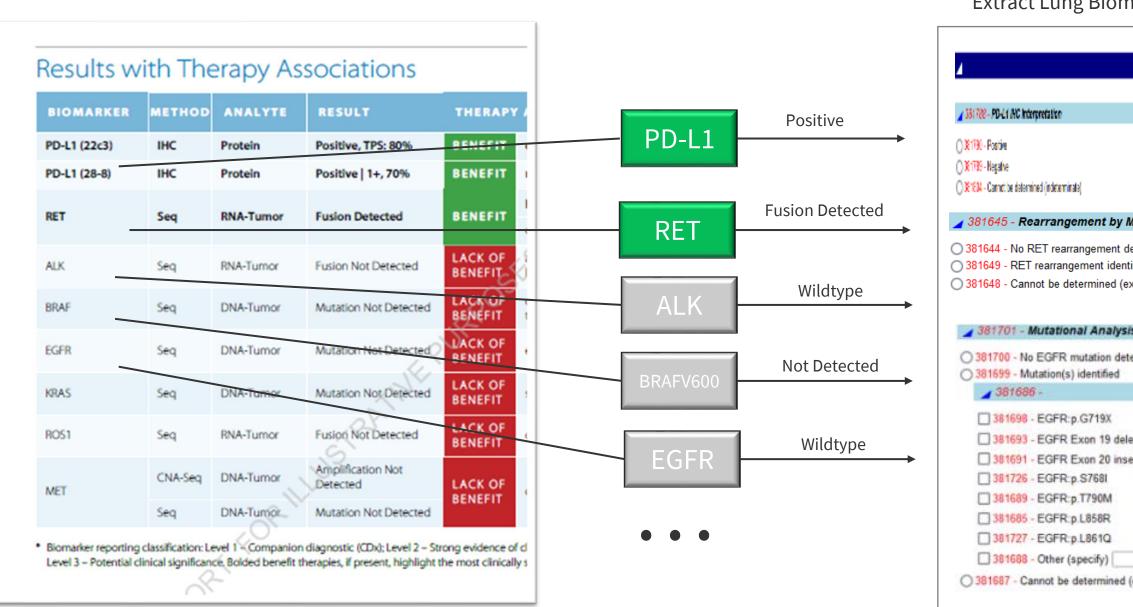
Caris Biomarker Results Auto-populate CAP eCP in mTuitive eFRM



- 1. Pathologist or other provider orders test from Caris via normal channels.
- 2. Caris performs lung biomarker test suite.
- 3. Caris sends |SON results to mTuitive Results Web Service.
- mTuitive Results Web Service notifies pathologists that results are available using Microsoft Teams or another messaging medium.
- 5. The pathologist opens the AP LIS to the specified case and begins a synoptic report using the Lung Biomarkers eCP.
- 6. eFRM looks up results and populates the CAP protocol with test results, avoiding onerous, redundant, error-prone data entry.
- 7. The pathologist continues to augment the report with additional interpretation, and submits.



Pertinent Information is Automatically Extracted From the Caris **Report to CAP Synoptic Report**







Extract Lung Biomarker Reporting Template

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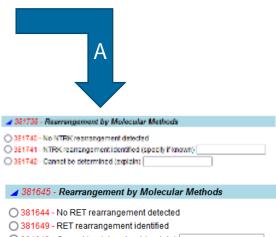
Caris Data is Delivered to mTuitive in JSON Format

Pathogenic Mutations

Wildtype or Biomarkers Not Detected

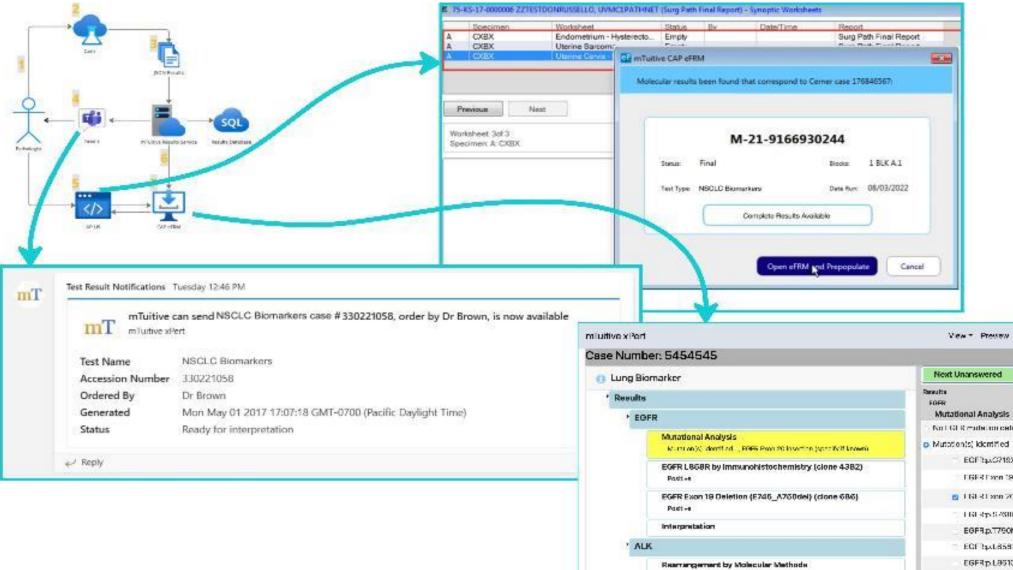






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Caris Biomarker Results Auto-populate CAP eCP in mTuitive eFRM



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Caris Biomarker Results Auto-populate CAP eCP in mTuitive eFRM

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Untreated diagnostic specimen	EGFR Exon 19 Deletion (E746_A750del) (clone 6B6): Negative ALK			
Results	Rearrangement by Molecular Methods: No ALK rearrangement detected			
• EGFR	ALK Immunohistochemistry: Negative RET			
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EGFR Exon 19 Deletion (E748_A750 Negative	Mutational Analysis: Mutation(s) identified - BRAF:p.V600E NTRK			
Interpretation	Rearrangement by Molecular Methods: No NTRK rearrangement detected NTRK by Immunohistochemistry: Negative			
ALK	PD-L1 IHC Interpretation: Positive			
Rearrangement by Molecular Metho No ALK rearrangement detected	CAP eCC November 2021 Release			
ALK Immunohistochemistry Negative	Close Copy To Clipbo	ard		
Interpretation		3)		



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Summary

- **Precision oncology** improves patient outcomes.
- Molecular profiling of **biomarkers** is central to precision oncology.
- **Comprehensive molecular profiling** offers the most in-depth molecular insights, enabling pathologists to gather all relevant information in one go without the need for duplicative testing.

- **Rapid growth** in biomarkers and biomarker testing is driving innovation in reporting.
- **Synoptic reporting** ensures patients get the correct workup and all data is gathered appropriately.
- **Auto-populating** the eCP with reference lab results and integrating the local LIS with the eCP can simplify workload, enabling pathologists to report within their workflow.

- Caris is collaborating with CAP to develop a method for **automatic population** of synoptic report fields with comprehensive molecular profiling results.
- CAP has begun discussions with two possible **test sites** (Banner University Health Phoenix, AZ, and Georgetown University School of Medicine, Washington, DC).
- **Further refinement** of and/or parsing to the CAP Biomarker Reporting Protocols may be necessary to capture relevant results.



Collaborators

Caris Life Sciences

- Matthew Oberley, MD, PhD, Senior Vice President, Executive Medical Director
- Jared Cotta, MPH, Head of Precision Oncology Programs

mTuitive, Inc

- Peter O'Toole, President & Chief Software Architect
- Colin Murphy, Chief Executive Officer

CAP Cancer Protocols and Data Standards Staff

- John Bodner, PhD: Clinical Content Manager
- Eric Daley, MS PA (ASCP)CM: Senior Clinical **Product Manager**
- Anna Patel, MS MSc: Molecular Content Manager
- Colleen Hebert, DHA: Clinical Quality Manager
- Keren Hulkower, PhD: Senior Clinical Release Manager
- Ted Carithers: Director, Cancer Protocols and Data Standards





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The Future of Cancer Data: **Unlocking Insights With Pathology Reporting Summit** October 6, 2023