Methylated Circulating Tumor DNA (mctDNA) in Colorectal Cancer
Market Insight

Summary of Colorectal Oncologist and Surgeon Interviews

September, 2018

Health Care
PRODUCT INTELLIGENCE

Introduction and Methodology

- The purpose of this document is to present findings of physician interviews regarding Methylated Circulating Tumor DNA (mctDNA) for use in detecting Colorectal Cancer disease recurrence and minimal residual disease.
  - Clinical data from Clinical Genomics' Colvera Product were provided to clinicians during interviews
- 40 Clinicians Treating Colorectal Cancer were interviewed between August and September, 2018 to gain perspective of early adoption of a mctDNA Product for use in CRC Recurrence Monitoring and Minimal Disease Detection (MRD)
  - 20 CRC Oncologists
  - 20 CRC Surgeons

Health Care
PRODUCT INTELLIGENCE

Executive Summary: Early Adoption

Surgeons Demonstrated Greater Willingness to Adopt CRC mctDNA Early vs. Oncologists

% Indicating Likely Behavior

	Oncologists	Surgeons	
	Recurrence Monitoring	MRD	Recurrence Monitoring
• No: • Wait for Longitudinal Studies • Wait for Inclusion in Guidelines	65%	18%	15%
• Maybe: • Conduct Evaluation	10%	18%	15%
• Yes: • Begin Sending Samples	25%	64%	70%

Health Care
PRODUCT INTELLIGENCE

Executive Summary: Annual Patient Loads

	Oncologists	Surgeons	
	Recurrence Monitoring	MRD	Recurrence Monitoring
Patients	72	146	98[(1)]

(1) Average for Surgeons actually performing Recurrence Monitoring. Only 57% of Surgeons performing Recurrence Monitoring

Health Care
PRODUCT INTELLIGENCE

Data Provided to MDs in Interviews

Presence of methylation genes in cancer vs. non-cancer tissue

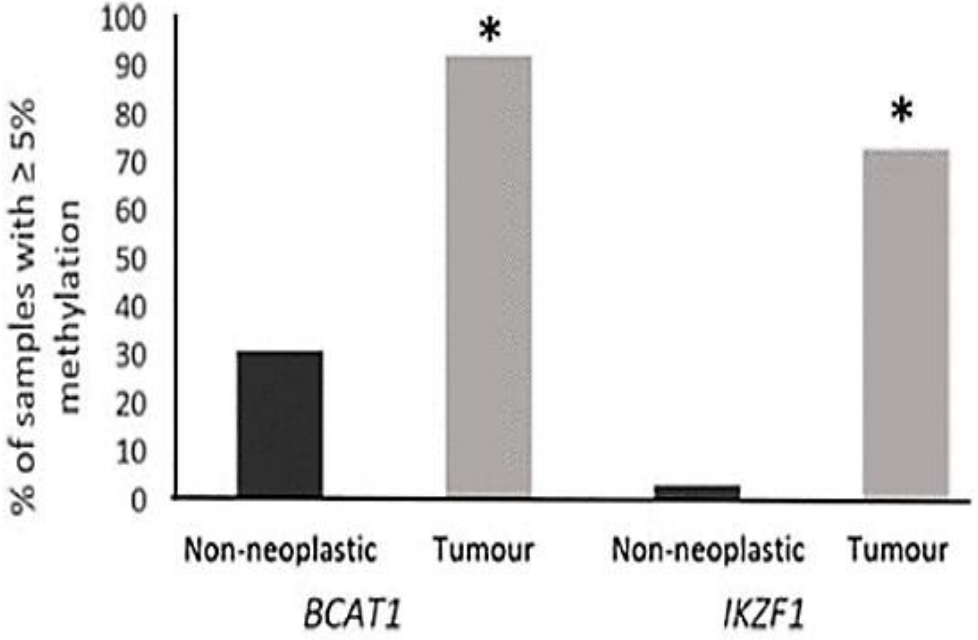


Figure 1. The proportions of tumour and non-neoplastic tissues with methylated *BCAT1* and *IKZF1* (n = 36). Samples were considered to have significant levels of methylation when levels were ≥5%. *$P < .05$ compared with non-neoplastic results.

- Significantly higher methylation of either *BACT1* or *IKZF1* seen in up to 92% (84/91) of CRC cancer tissues compared to up to 30% in non-neoplastic specimens
- Tissue methylation levels were independent of cancer stage

Source: Jedi et al. Methylation and Gene Expression of BCAT1 and IKZF1 in Colorectal Cancer Tissues. Clinical Medicine Insights: Oncology, 10 May 2018.

Health Care
PRODUCT INTELLIGENCE

Methylated circulating tumor derived DNA vs. CEA for detection of recurrent Colorectal Cancer

mctDNA test picked up 2x as many true recurrent cases vs. CEA

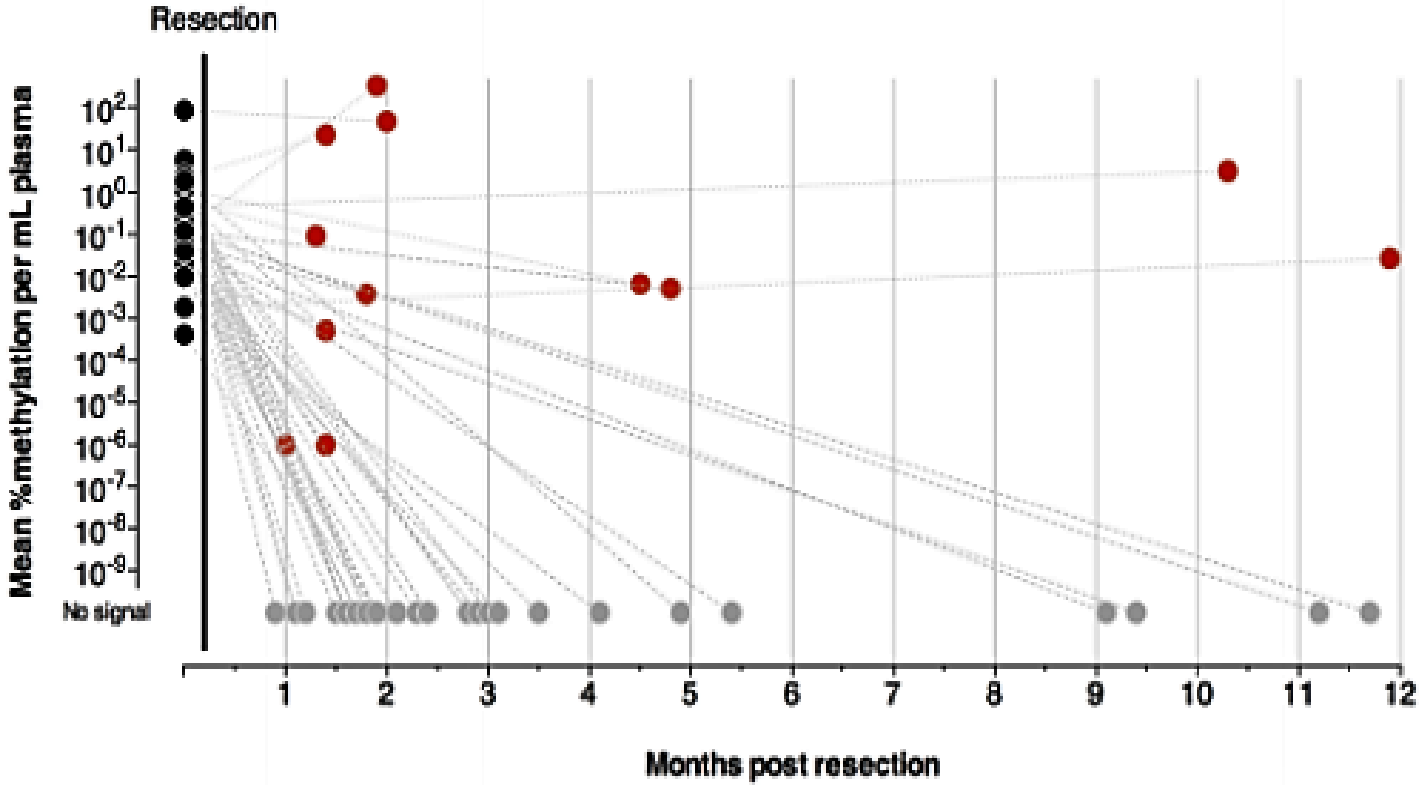
All Cases = 122		M-ctDNA[1] Positive		CEA Positive	
Recurrence					
Local	4	3	75%	2	50%
Distant	24	16	67%	7	29%
Total	28	19	68%	9	32%
No Recurrence	94	12	13%	6	6%

[1] Methylated circulating tumor markers BCAT1 and IK7F1
Source: Young, GP et al Cancer Medicine, 2016

Health Care
PRODUCT INTELLIGENCE

Effect of Resection on mctDNA

Of 47 patients mctDNA-positive at before CRC cancer surgery, 35 (74.5%) became negative after resection



Key: Black circles: mctDNA positive cases before resection (n=47)
Red circles: cases who tested positive after resection (n=12)
Grey circles: cases who tested negative after resection

Health Care
PRODUCT INTELLIGENCE

Oncologists

Health Care
PRODUCT INTELLIGENCE

Oncologist Demographics

- When do you typically begin treating patients:
  - 81% gave as #1 response: After Surgery
  - About half of total respondents also indicated they received some patients prior to surgery (referral by Gastroenterologists)
  - 5% treat metastatic disease only

Oncologists: Recurrence Monitoring

	Average Number Patients Monitored Annually	% Using CEA to Monitor
Stage 1(1)	7	72%
Stage 2	16	100%
Stage 3	25	100%
Stage 4	23	100%
Total	72	

(1) Because Stage 1 patients do not receive Chemo, many Stage 1 patients NEVER see an Oncologist

33% of Oncologists are monitoring NO Stage 1 Patients. As a result, Stage 1 recurrence monitoring tends to fall to Surgeons

Health Care
PRODUCT INTELLIGENCE

Oncologists: Recurrence Monitoring

Frequency of Patient Monitoring using CEA

- Stage 1 : Annual
- Stages 2-3: Every 4-6 months for first 2 years
  Every 6 months for following 3 years
- Stage 4: Every 3 months

Oncologists: Comments

- “Just because we can pick something up earlier may not help”
- “The question is, are we picking up something earlier that will lead to a better outcome?”
- “Because early recurrence almost predictably will happen in the liver where it can be surgically removed, a certain (low) percentage of those patients can be cured”
- “I don’t think capturing micrometastatic disease and jumping on chemotherapy earlier is going to lead to any more cures”
- “False positives too high” (Several mentions)
- “High false positive rate will translate into a lot of unnecessary CT and PET scans”
- “They were doing ctDNA for breast cancer…there was no sense of direction what to do with the result. If you have that answer, it will be a game changer”

Health Care
PRODUCT INTELLIGENCE

Oncologists: Early Adopters

- No: 65%
  - Wait for Longitudinal Studies
  - Wait for Inclusion in Guidelines
- Maybe: 10%
  - Send a few samples
- Yes: 25%
  - Begin Sending Samples

Health Care
PRODUCT INTELLIGENCE

Surgeons

Health Care
PRODUCT INTELLIGENCE

Surgeon Demographics

- When do you typically begin CRC treating patients:
  - Post-Colonoscopy (Referred by Gastroenterologists): 85%
  - Cancer found via Colonoscopies performed by Surgeon: 15%
- Average number of CRC Related Surgeries:
  - Monthly: 12
  - Annually: 144

Surgeon Practices

- Pre-Surgery Testing Performed on CRC Patients
  - CEA 100% (1)
  - CT Scan 100%

- CEA Repeated After Surgery
  - Yes 13%
  - Sometimes(2) 13%
  - No 74%

(1) All Stages (2) When CEA is high and not sure why

Health Care
PRODUCT INTELLIGENCE

Minimal Disease Detection (MRD) Generally Not Performed for CRC

- Discussion regarding MRD typically involves answers to questions:
  1. What do you do to detect MRD?
     - Pathology (# positive lymph nodes)
     - “There isn’t any good protocol to diagnose residual disease”
     - Any potential MRD evidence seen as supporting treatment decision and probability of recurrence determination; presented at Tumor Board discussions.
  2. When do you repeat CEA following Surgery?
     - 3 months (first surveillance appointment)

- Conclusion: Lack of tools to reliably predict CRC MRD has resulted in general absence of MRD detection in clinical practice

Health Care
PRODUCT INTELLIGENCE

Surgeons: Commentary Regarding MRD Detection

- “Micro residual disease is not that common, however, maybe we’ll find things we didn’t anticipate.”
- “Micro-mets don’t secrete CEA of any consequence, so CEA was never a great detector of micro residual disease.”
- “Follow-up (to surgery) depends on how aggressive the disease is.”
- “If we are going to be looking at elevated levels in patients that may not truly have residual disease, which could potentially lead down the road of rather expensive testing with PET CT’s which would ordinarily not be ordered and potential surgical intervention that you may not otherwise undertake. I think for the most part these endeavors would be fruitful. I would be concerned that we would be overtreating some patients. I would like to see better data on it for specificity so we know we are not doing any harm or needlessly wasting Health Care resources due to a diagnosis that might not be there.”

Despite no standard practice for CRC MRD, Surgeons are nevertheless willing to use the mctDNA test as a tool for MRD

Surgeons: Early Adopters for MRD

- No: 18%
  - Wait for Longitudinal Studies
  - Wait for Inclusion in Guidelines
- Maybe: 18%
  - Send a few samples
- Yes: 64%
  - Begin Sending Samples

Health Care
PRODUCT INTELLIGENCE

Surgeons: Early Adopters for MRD

- Proportion of Surgeries Would Test with mctDNA? 66%

- What CRC Stages would you test?
  - All stages 56%
  - Stages 1-3 only 22%
  - Stages 2-3 only 22%

Health Care
PRODUCT INTELLIGENCE

Surgeons: Early Adopters for MRD

- Given lack of MRD expertise, companies marketing mctDNA tests will want to encourage experimentation AND provide as much guidance as possible in MRD use
  - Important to give suggested guidelines for use
    - For example, 1 sample draw prior to surgery, another X time after surgery
- Most Surgeons see the potential for mctDNA for MRD a tool to uncover hidden information about the patient's case:
  - Residual disease at the site of the primary tumor
  - Residual disease in lymph nodes
  - Occult Metastases
- "All would change treatment pretty dramatically"

Surgeons also do a fair amount of CRC Surveillance/ Recurrence Monitoring

Surgeons Performing CRC Surveillance/Recurrence Monitoring

Surgeon Does No Surveillance	43%
Surgeon Does Surveillance Stage 1 Only	7%
Surgeon Does Surveillance Stages 1-2 Only	21%
Surgeon Does Surveillance Stage 1-3 Only	21%
Surgeon Does Surveillance Stage All Stages	7%

Health Care
PRODUCT INTELLIGENCE

Surgeons: Recurrence Monitoring

	Average Number Patients Monitored Annually	% Using CEA to Monitor
Stage 1	29	73%
Stage 2	33	100%
Stage 3	32	100%
Stage 4	4	100%
Total	98 (1)	

(1) For Surgeons peforming Recurrence Monitoring

Health Care
PRODUCT INTELLIGENCE

Surgeon/Oncologist Interaction During CRC Patient Surveillance

- Decisions regarding whom (Oncologist or Surgeon) will perform Recurrence Monitoring Surveillance are situational
  - Often Surgeons perform Stage 1 Surveillance because these patients never reach Oncologist
  - Generally, any patients not being monitored for Recurrence by an Oncologist are picked up by Surgeon, who sees CRC patients at regular intervals
  - Oncologists generally order blood work on Surveillance patients they see
  - Surgeons receive and review any blood work or scans Oncologists order

- However, if Surgeon feels they should offer some type of service (e.g. PET scan following rising CEA level) the Surgeon will take action

Surgeons: Early Adopters for Recurrence Monitoring

- No: 15%
  - Wait for Longitudinal Studies
  - Wait for Inclusion in Guidelines
- Maybe: 15%
  - Send a few samples
- Yes: 70%
  - Begin Sending Samples

More than half of all Surgeons who would start sending in samples currently do NO Recurrence Monitoring!

Health Care
PRODUCT INTELLIGENCE

Surgeon: Comments

- “Oncologists are not the only ones who take care of these patients – surgeons take care of a lot of these patients too”
- “CEA sometimes leaves us scratching our head. It can come back normal for patients with metastatic colon cancer. It’s not a great test. If you could show that this (mctDNA) test was better….then it’s got to work tis way into the guidelines.”
- “This (mctDNA) test result could become the centerpiece of an office visit. The primary reason for a patient visit is to determine progression.”
- “This may be the test we’ve been waiting for.”

Health Care
PRODUCT INTELLIGENCE

Concerns: Surgeons and Oncologists

- False positives
- Larger data sets
- What will this do to change the way patient is managed?
- What will this do to increase survival?