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EDITORIAL

Can molecular biomarkers replace a clinical risk score for resectable colorectal liver metastasis?

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Abstract

In resectable colorectal liver metastasis (CRLM) the role and use of molecular biomarkers is still controversial. Several biomarkers have been linked to clinical outcomes in CRLM, but none have so far become routine for clinical decision making. For several reasons, the clinical risk score appears to no longer hold the same predictive value. Some of the reasons include the ever expanding indications for liver resection, which now increasingly tend to involve extrahepatic disease, such as lung metastases (both resectable and non-resectable) and the shift in indication from "what is taken out" (*e.g.*, how much liver has to be resected) to "what is left behind" (that is, how much functional liver tissue the patient has after resection). The latter is amenable to modifications by using adjunct techniques of portal vein embolization and the associating liver partition and portal vein ligation for staged hepatectomy techniques to expand indications for liver resection. Added to this complexity is the increasing number of molecular markers, which appear to hold important prognostic and predictive information, for which some will be discussed here. Beyond characteristics of tissue-based genomic profiles will be liquid biopsies derived from circulating tumor cells and cell-free circulating tumor DNA in the blood. These markers are present in the peripheral circulation in the majority of patients with metastatic cancer disease. Circulating biomarkers may represent more readily available methods to monitor, characterize and predict cancer biology with future implications for cancer care.

Key words: Colorectal cancer; Liver metastasis; *KRAS*; Disease-free survival; Circulating tumor cell; Liver surgery; Overall survival; Molecular biomarkers

Core tip: As a general rule, "good" colorectal liver metastasis (CRLM) cases amenable for surgery have fewer bad

genetic traits, such as less likelihood for *BRAF* mutations or *KRAS* mutations. *KRAS* mutation in patients with resectable CRLM suggests a more aggressive disease with shorter progression free and overall survival. Emerging evidence suggest that tumors change during the course of treatment and, thus giving way to new clones that may be of a different genetic makeup and have a different resistance pattern. Thus, new ways of monitoring disease and markers of progression is needed, including circulating cancer biomarkers and tissue-based genetic profiles.

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INTRODUCTION

Colorectal cancer (CRC) is a leading cause of cancer deaths in the western world. For patients with non-metastatic disease at diagnosis, the prognosis for disease-free as well as overall survival (OS) is very good and, currently, exceeding 60% for both colon and rectum cancer[1]. Yet, still, some 40% will develop metastasis and die from the disease. Furthermore, about 20%-25% present with metastasis at the time of diagnosis, of which only a minority will be amenable to attempt at curative resection for both primary and metastatic disease. The liver is the most frequent site of metastasis in both situations, followed by the lungs and peritoneum. The current use of the TNM system as a guide of adjuvant therapies and prognosis is imperfect at best and is heavily debated[2], emphasised by the need for continuous updates (now in its 8th edition). Notably, there is a strong need for better understanding of which tumours will develop metastasis and how cancer cells are able to invade, escape, colonize and grow as distant metastasis. Further, when metastases are present, better knowledge of what therapy can be used and how the cancer biology can be influenced, is direly needed.

For unresectable metastatic CRC disease the OS has dramatically changed over the past few decades. The improved survival is due to changes in chemotherapy and targeted drugs. A median survival historically reported around 6 mo for best supportive care alone is now approaching 24 mo and above with currently available chemo-regimens and targeted therapy[3]. Importantly, RAS profiling has emerged as an important predictive and prognostic factor, with *KRAS* and *BRAF* mutants displaying poor prognosis. In stage Ⅳ disease, targeted therapy (EGFR directed drugs[4]) is implemented in clinical practice and knowledge of mutated pathways is actively used to shape design of new trials, with recent guidelines for extended RAS testing being launched[5].

Conversely, in resectable colorectal liver metastasis (CRLM) the role and use of molecular biomarkers is more controversial. Several biomarkers have been linked to clinical outcomes in CRC, but none have so far become important in classification of cancer stage or in determining oncological or surgical treatment of the tumour or metastasis. Notably, as knowledge of tumor biology has increased, so has the emergence of molecular markers also come of age.

Currently, 5-year survival rates in patients with resectable CRLM ranges from 25% to 40% dependent on inclusion criteria and selection of cohorts. Several past studies have been published in an attempt to identify risk factors and predict survival. The scoring systems vary in terms of its clinical use, but risk factors include synchronous liver disease, primary tumor node status and histology, number and size of liver metastases, CEA level, disease-free interval and presence of extrahepatic disease[6-8]. The most widely used clinical scoring system is that proposed by Fong *et al*[8], as depicted in Table 1. For scores 1-2, surgery for CRLM was clearly recommended, but for patients with scores of 5, the benefit was deemed questionable. Notably, the authors argued in their seminal paper, that to make the scoring system widely applicable, the additional inclusion of cellular or genetic markers was not reasonable. The latter prediction may have changed with more widespread molecular laboratories and considerable reduction in unit costs for molecular analyses.

For several reasons, the clinical risk score appears to no longer hold the same predictive value in current evaluation and management of CRLM. Some of the reasons include the ever expanding indications for liver resection, which now increasingly tend to involve extrahepatic disease, such as lung metastases[9] (both resectable and non-resectable) and the shift from "what is taken out" (*e.g.*, how much liver has to be resected) towards "what is left bind" (that is, how much functional liver tissue is the patient left with), the latter for which adjunct techniques of portal vein embolization[10] and the associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) techniques[11] have continued to expand indications for liver resection. Added to this complexity is the increasing number of molecular markers, which appear to hold prognostic and predictive information, for which some will be discussed here.

ROLE OF *KRAS* IN RESECTED CRLM

Up to 30%-40% of patients with CRC have mutated *KRAS*. The frequency for mutated *KRAS* in CRLM corresponds well with that of the primary tumour[12]. The incidence of *KRAS* mutation in resectable CRLM is variable, and in one meta-analysis reported a frequency between 15% and 37%[12], likely indicating differences in selection criteria for CRLM surgery among the studies[13]. The meta-analysis included 14 studies with a total of 1809 patients[12]. Eight studies reported OS after resection of CRLM in 1181 patients. The mutation rate was 27.6%, and *KRAS* mutation was negatively associated with OS [hazard ratio (HR) = 2.24, 95%CI:

Table 1 The clinical risk score (as suggested by Fong *et al*[8])

Score	0	1	Predicted 5-yr survival
Nodal status of primary tumor (pN0 *vs* pN+)	-	+	
Disease-free interval[1]	> 12 mo	< 12 mo	
Number of tumors	⩽ 1	> 1	
Pre-operative CEA level	⩽ 200 ng/mL	> 200 ng/mL	
Size of largest tumor	⩽ 5 cm	> 5 cm	
Score			
0			60%
1			44%
2			40%
3			20%
4			25%
5			14%

[1]From primary tumor to discovery of liver metastasis. CEA: Carcino-embryonic antigen.

1.76-2.85]. Seven studies reported recurrence-free survival (RFS) after resection of CRLM in 906 patients. The mutation rate was 28.0%, and *KRAS* mutation was negatively associated with RFS (HR = 1.89, 95%CI: 1.54-2.32). Thus, there was an overall consistent poorer overall- and RFS for patients with mutated *KRAS* among the studies.

Still, the overall prognostic role of *KRAS* mutations is not clear. It seems that there is a higher rate of *KRAS* mutation in patients with extrahepatic metastasis and non-resectable CRLM[12,14], that there is a higher risk of subsequent recurrence in all sites (brain, bone, liver and lungs) for patients with *KRAS* mutations[15,16] and, that *KRAS* mutation in patients with resectable CRLM suggests a more aggressive disease with shorter progression free and OS[12]. Indeed, as shown[17], the difference in survival after liver resection was attributed to having either wild type *KRAS* or mutant *KRAS*, rather than achieving an R0 or R1 situation. This emphasizes the role of inherent cancer biology rather than resection margins. Factors that are associated with aggressive or advanced tumor biology (*e.g.*, bilobar disease, multiple metastasis, large metastasis, and metastasis in difficult locations) are also associated with technically complex cases and are as such being at higher risk for a potential R1 resection. These data therefor suggests that it is the cancer biology, and not the R1 resection, that is related to worse survival[17]. Similar results were showed in a study were recurrence-free and OS were examined after treatment for CRLM with liver resection followed by adjuvant hepatic arterial infusion and chemotherapy. Positive surgical resection margins (R1) were not found to significantly predict RFS[15], but rather, again, a decreased RFS occurred for *KRAS* mutant CRLMs. Furthermore, down-stream *BRAF* mutations in the RAS-pathway[4] signify a particularly poor prognosis in resected CRLM[18]. Thus, the clinical role of *KRAS* in resectable CRLM is slowly becoming clearer. In one recent study from the MD Anderson Cancer Center[19], the investigators found that patients with poor prognostic features, such as node-positive primary tumor (pN+), largest liver metastasis > 3 cm and who had > 7 cycles of preoperative chemotherapy in addition to *KRAS* mutation had a particularly poor prognosis. The authors conclude that major hepatectomy may be ill advised in such patients and that other therapeutic alternatives should be considered[19].

MOLECULAR MARKERS TO DEFINE "GOOD" FROM "BAD" BIOLOGY IN CRLM

In addition to mutations in the RAS-pathway, a plethora of known and new markers are considered as predictive and prognostic, yet few have found their way to clinical use. As a general rule, "good" CRLM cases amenable for surgery have fewer bad genetic traits, such as less likelihood for *BRAF* mutations or *KRAS* mutations. Adding to the complexity in understanding the role of genetic mutations and targeted therapy is the findings from the "new EPOC" study[20] of adjuvant chemotherapy with or without cetuximab (an EGFR inhibitor) to patients with resectable CRLM and *KRAS* wt. In theory, the drug should have a beneficial effect on outcomes, but to the investigators surprise, the group who received cetuximab actually had a worse RFS[20]. While the study has received critique for its design, conduct and analysis[21,22], the uncertainty linked to these results await further exploration and clarification. The jury is still out regarding the role of cetuximab for resectable CRLM in the adjuvant setting.

In CRC, presence of microsatellite instability (MSI) is known as a favourable genetic trait[23], yet with an emerging role for subtypes of such microsatellite alterations, including elevated alterations at selected tetranucleotide repeats (EMAST)[24]. One recent study[25] found that CRLM with a favourable outcome are more likely to have EMAST and low-frequency MSI (MSI-L). How this relates to other markers need to be further explored and validated in external series, but proves that molecular markers can aid in deciphering the cancer biology and thus possibly help predict outcomes[26]. Patients with concomitant liver and lung metastases have an "ugly" tumor biology and are more likely to have high frequencies

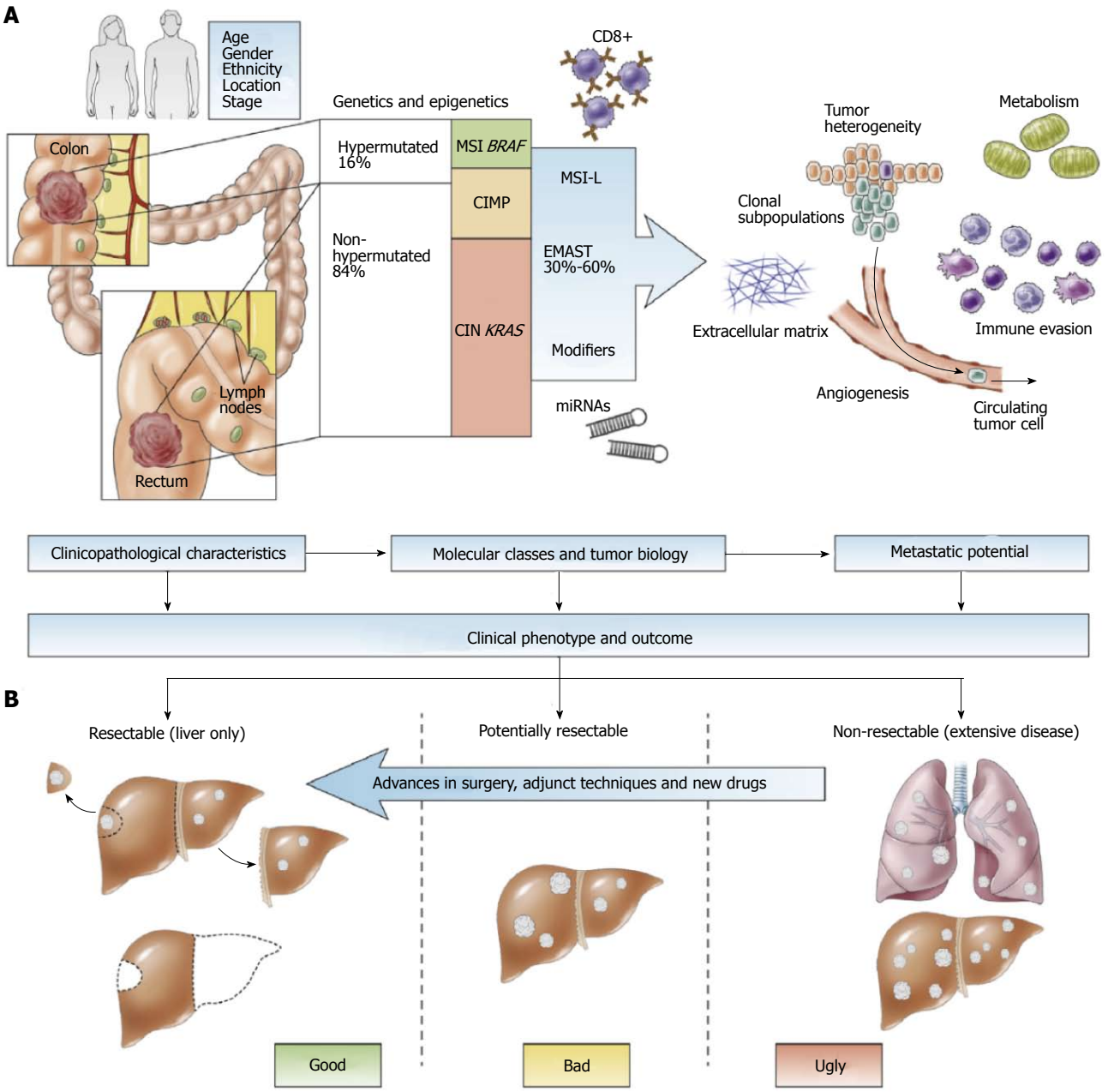

Figure 1 Clinical and molecular influence on cancer biology in colorectal liver metastases. A: Clinical behaviour of colorectal cancer is determined by several factors, including demographic data (age, gender, race) and tumor presentation (location, stage) and timing of presentation of metastasis (synchronous or metachronous). Embedded in the cancer cells are the molecular pathways, which follows distinct forms of genomic instability yet with partly overlapping areas. Hypermutated cancers belong to the microsatellite instable (MSI) cancers and in part the CpG-island methylator phenotype (CIMP) cancers. Non-hypermutated cancers follow in large parts the chromosomal instability (CIN)-driven pathways, often involving *KRAS* mutations from an early stage. The propensity to develop metastasis may possibly be modified through the elevated microsatellite alterations at selected tetranucleotide repeat (EMAST) and associated mechanisms, such as regulation of microRNAs or activity and numbers of $CD8^+$ immune cells. Finally, the microenvironment contains numerous factors that may facilitate or propagate metastasis to invade, spread and settle in a new organ sites, particularly the liver and the lungs; B: Determined by the clinical presentation, the genetic traits and molecular mechanisms, the prognosis in colorectal liver metastasis is related to resectabilty for long-term survival. Reprinted from Søreide K, Watson MM, Hagland HR. Deciphering the Molecular Code to Colorectal Liver Metastasis Biology Through Microsatellite Alterations and Allelic Loss: The Good, the Bad, and the Ugly. *Gastroenterology* 2016 Apr; **150** (4): 811-814, Copyright (2016), with permission from Elsevier.

of both *KRAS* and *BRAF* mutations and respond poorly to any line of treatment (Figure 1). The "bad" cases are considered as "in between" - where the current shift from "nonresectable" to "resectable" experiences a drift with changing practice in surgical strategy, novel techniques and use of conversion chemotherapy regimens to detect responders and improve outcomes. Novel biomarkers may aid in understanding aggressiveness of CRLM, assist in clinical decision-making and help to find new and more efficient therapies.

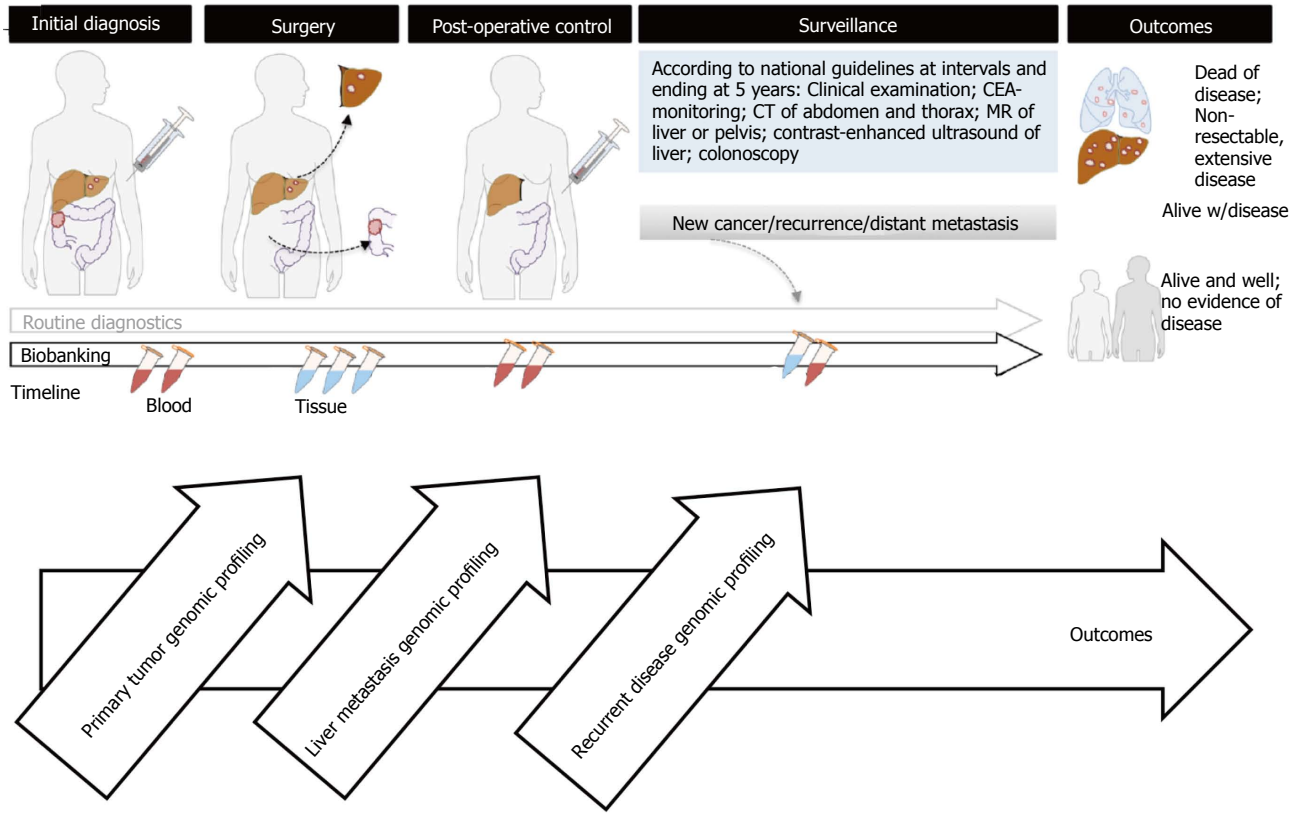

Figure 2 Translational cancer research design for investigation of cancer biology. The illustration is based on the ACROBATICC (Assessment of Clinically Related Outcomes and Biomarker Analysis for Translational Integration in Colorectal Cancer) project flow, see main article for details. Reproduced with permission from Søreide *et al*[39]. *J Transl Med* 2016; **14** (1): 192. © 2016 Søreide *et al*. CEA: Carcino-embryonic antigen; CT: Computed tomography; MR: Magnetic resonance.

LIQUID BIOPSIES: CIRCULATING TUMOR CELLS AND CIRCULATING TUMOR DNA

While several of the genetic markers may bear prognostic info and may be a valuable source for further decision-making after resection, there is a problem with having to explore tissues after surgery is first done. Emerging evidence suggest that tumors change during the course of treatment and, thus giving way to new clones that may be of a different genetic makeup and have a different resistance pattern[27-29]. Consequently, finding methods where disease determinants can be found prior to resection would be beneficial. Further, being able to base such info on "liquid biopsies" (*e.g.*, blood test, serum samples or the like) rather than tissue biopsy is an attractive approach.

Circulating tumor cells (CTCs) are cells present in the peripheral circulation in the majority of patients with metastatic cancer disease. Similarly, most cancers shed cell-free circulating tumor DNA (ctDNA) in the blood[30]. ctDNA can be analyzed to generate molecular profiles which capture the heterogeneity of the disease more comprehensively then tumor tissue biopsies. This approach commonly called "liquid biopsy" can be applied to monitor response to therapy, to assess minimal residual disease and to uncover the emergence of drug resistance. However, technological shortcomings and difficulty in finding the perfect markers to identify such CTCs or ctDNA have resulted in few studies of any clinically valuable difference in terms of survival outcomes or prediction[31]. Other studies appear promising, including one recent meta-analysis on the prognostic role of ctDNA[32], also for disease prediction but are small and need further validation[33-35].

What appears essential though for tumor biology is that in the majority of the patients, CTCs reflected the molecular characteristics of metastatic cells better than the primary tumors[36]. Also, metastases appear to shed new cells of an invasive type, thus giving further rise to the metastatic tumor phenotype[37]. Remaining challenges is the isolation and characterization of CTCs and the sensitivity and specificity in detection of ctDNA[38]. Thus, CTC-, and ctDNA-based liquid biopsies may not be widely adopted for routine cancer patient care until the suitability, accuracy, and reliability of these tests are validated and more standardized protocols are corroborated in large, independent, prospectively designed trials. As technology is refined and better and more accurate markers validated, there is likely to be an increasing role for circulating markers in the future.

CONCLUSIONS AND WAY FORWARD

Currently, clinicians will still heavily rely on the clinical features and disease presentations of patients with CRLM. However, as aggressive treatment regimens progress, new

technology make more patients amendable for resection and as an increasing number of patients are diagnosed and considered in a synchronous setting, the need for better predictors of outcome becomes increasingly important. There is a continued need for better studies, with proper design for biomarker research, with findings of interest and importance that need to be evaluated in test-sets and validation cohorts. External validation in cohorts derived outside the index institution should be sought in order to explore and define generalizability and validity. Biobanking and biopsies should preferably include the course of disease, from primary tumor to metastatic disease to recurrence, with samples including recurrence-free intervals or samples taken during change in chemoregimens. Only then can the natural course and clonal evolution of cancer be explored and proper therapy initiated. However, most studies do not have the opportunity to do this at the moment, most often restricted by logistics, funding and investigator initiatives. In our own prospective translational cancer cohort[39] we seek to obtain blood samples and tissue samples from all CRC and CRLM resected within a defined population (Figure 2). This is done with the hopes of having samples that can identify tissue- or serum-based markers of disease-specific outcomes. Hopefully, this may in the near future move us away from clinical risk scores alone, to more precise molecular markers in the genomic era. Truly, to overcome cancer as a disease, the key to success lies in better understanding of the cancer biology. To paraphrase the surgeon oncologist Blake Cady[40]: "Biology is King; selection of cases is Queen, and the technical details of surgical procedures are Princes and Princesses of the realm who frequently try to overthrow the powerful forces of the King and Queen, usually to no long-term avail, although with some temporary apparent victories".

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