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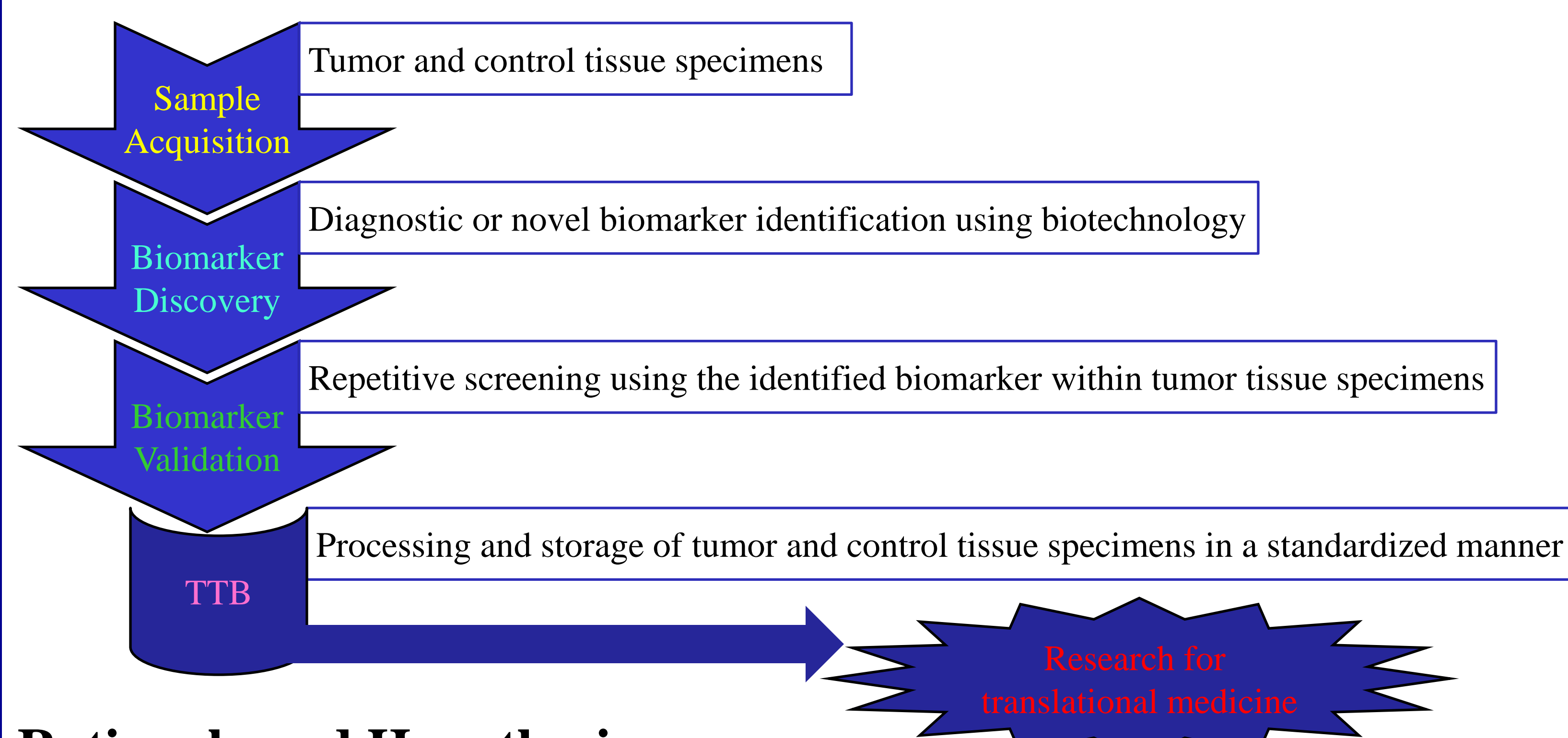
## Abstract:

Translational medicine integrates biomedical research with clinical and diagnostic strategies to improve health. A resourceful tool of translational medicine in the field of oncology is tumor tissue biobanking. Tumor tissue biobanking is used for biomedical research for the discovery of diagnostic and prognostic biomarkers that could provide insight into disease treatment and prevention. The presented case demonstrates that tumor tissue biobanking serves as a valuable resource for identifying diagnostic and prognostic biomarkers of colorectal cancer from a series of colorectal adenocarcinoma tissue specimens. In these tissue specimens, mutated oncogenic BRAF and microsatellite instability were associated with a poor clinical features and patient prognosis.

## Background:

Tumor tissue biobanking (TTB) plays a major role in translational medicine by serving as a resource for biomedical research that aids clinicians in patient diagnosis and the development of therapeutic strategies. Such feats are accomplished by TTB through the discovery of diagnostic cancer-predictive biomarkers or novel biomarkers that are characteristic of a particular mutational and pathological status within a tumor tissue sample. This is derived from a spectrum of archived TTB samples that are associated with a series of data, which constitutes immunohistochemical, proteomic, microarray expression, sequencing, and genotyping analysis. As anticipated, this process relies on histotechnology for providing the service of processing, preservation, and histological analysis of TTB samples. The process of identifying and characterizing a diagnostic biomarker from tumor tissue for TTB is depicted in the **schematic** below. This process entails the acquisition of tumor and control tissue specimens, which can be allocated from TTB, the discovery of a diagnostic or novel biomarker within the tumor tissue sample using biotechnological approaches, and validation of the biomarker using repetitive screening within tumor tissue samples. The study of these TTB specimens will ultimately allow the clinician to perform surveillance of early stages of the disease and choose a particular therapy that will prevent the development of malignant cancer and have the best outcome for the patient (1-3). The broad implication of this process is etiological insight into pathogenesis of cancer and disease prevention.

TTB can help in understanding the pathogenesis and progression of colorectal cancer. This disease entails a series of mutations in tumor suppressive genes, such as p53, or oncogenes, such as KRAS or BRAF, that promote genomic instability and tumorigenesis. It is important that a clinician may use this mutational status to strategize an effective therapy (3-5).



## Rationale and Hypothesis:

TTB provides a resource for studying and correlating a mutational status of colorectal tumors with the clinical features, prognostic outcome, and response of therapy of the patient. The current case examines the clinical pathology and prognosis from colorectal tumor samples from TTB that contain a particular mutational status, such as an oncogenic BRAF mutation. TTB in this case has a role in translational medicine by characterizing BRAF in tumor tissues as a predictive biomarker for genomic instability, tumorigenesis, and a poor patient prognostic outcome (5).

## Methodology:

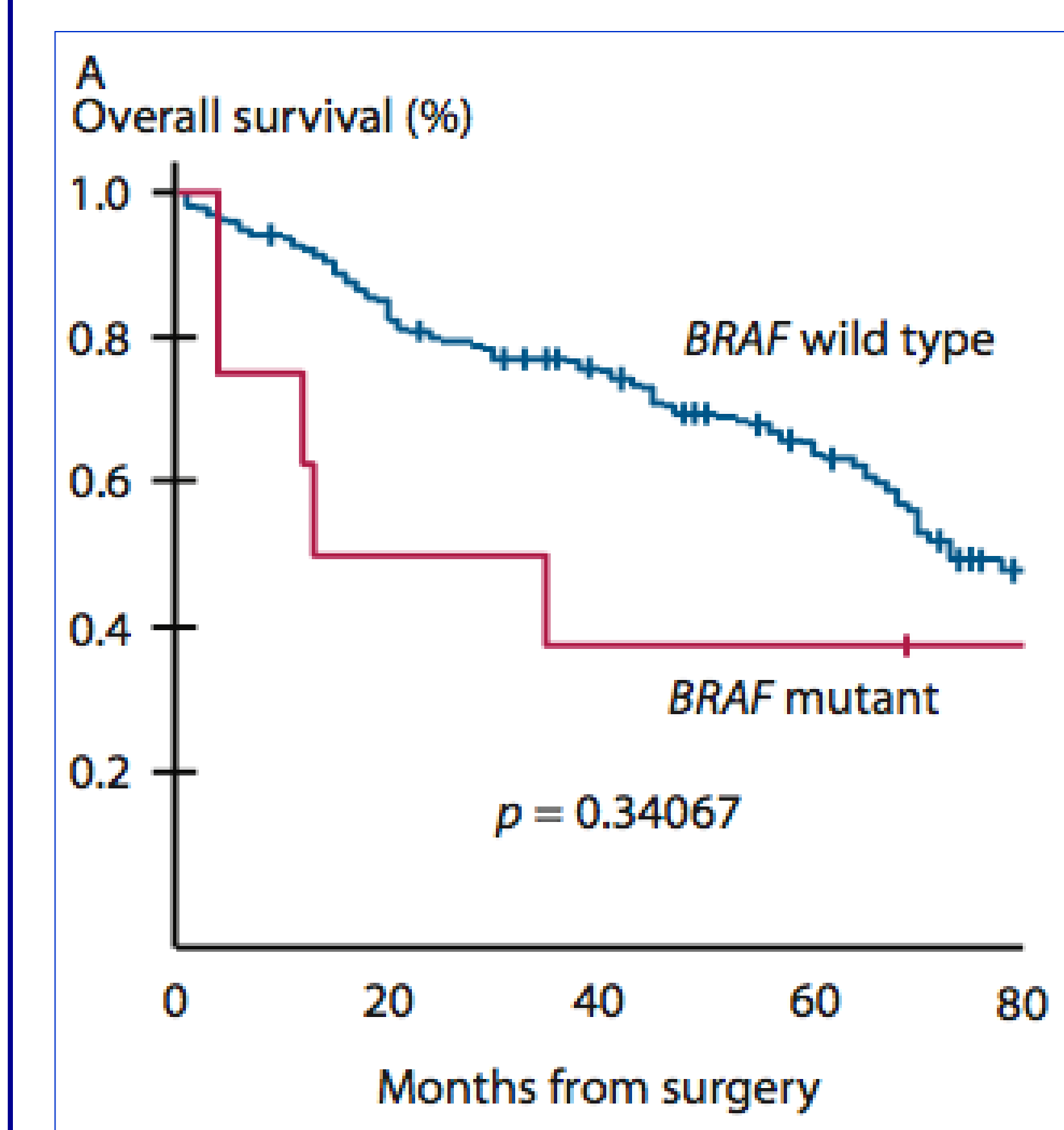
Frozen TTB specimens that were colorectal adenocarcinomas collected between the years 2000 and 2009 were analyzed for mutations in the BRAF oncogene from a study population of 475 patients. BRAF mutations were detected using DNA sequencing and polymerase chain reaction. Genomic instability, a downstream effect of a BRAF mutation, was determined using microsatellite instability testing. Statistical analysis entail a Fisher exact and  $\chi^2$  tests (5).

## Results:

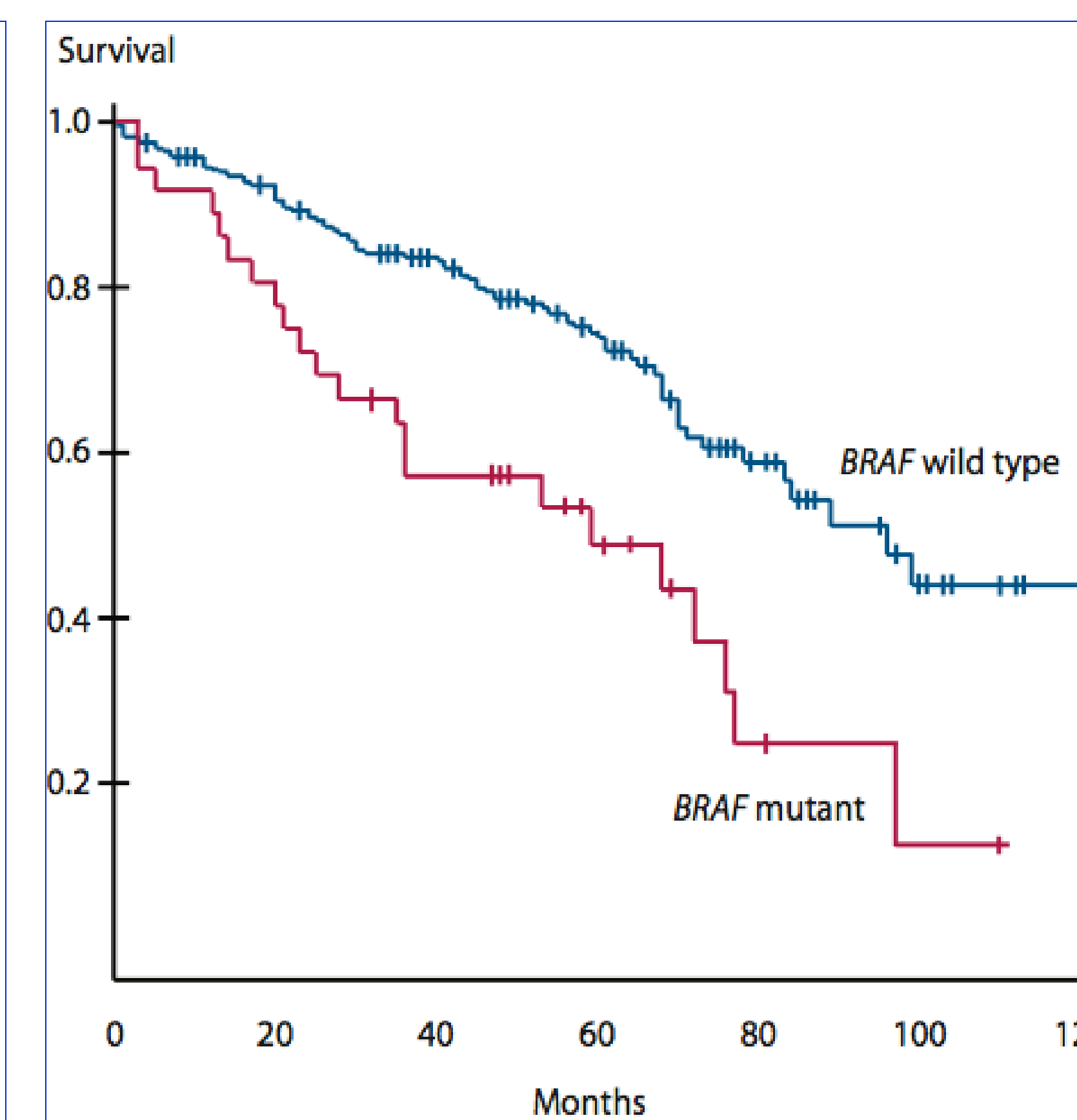
	BRAF wild type	BRAF mutant	p
No. of patients	419 (88%)	56 (12%)	
Age, median (range)	66 (18-93)	75 (52-94)	0.004
Sex			
Male	235 (56%)	16 (29%)	<0.001
Female	184 (44%)	40 (71%)	
Tumor location			
Proximal	184 (44%)	53 (95%)	<0.001
Distal	98 (23%)	3 (5%)	
Rectum	137 (33%)	0 (0%)	
Differentiation			0.014
Well	20 (5%)	1 (2%)	
Moderate	301 (72%)	32 (57%)	
Poor	98 (23%)	23 (41%)	
Stage			0.751
I	77 (18%)	10 (18%)	
II	144 (34%)	23 (41%)	
III	146 (35%)	16 (29%)	
IV	52 (12%)	7 (12%)	
MSI-H*	47/298 (16%)	29/38 (76%)	<0.001

MSI-H = microsatellite instability high.  
\*Note MSI status available on 336 patients.

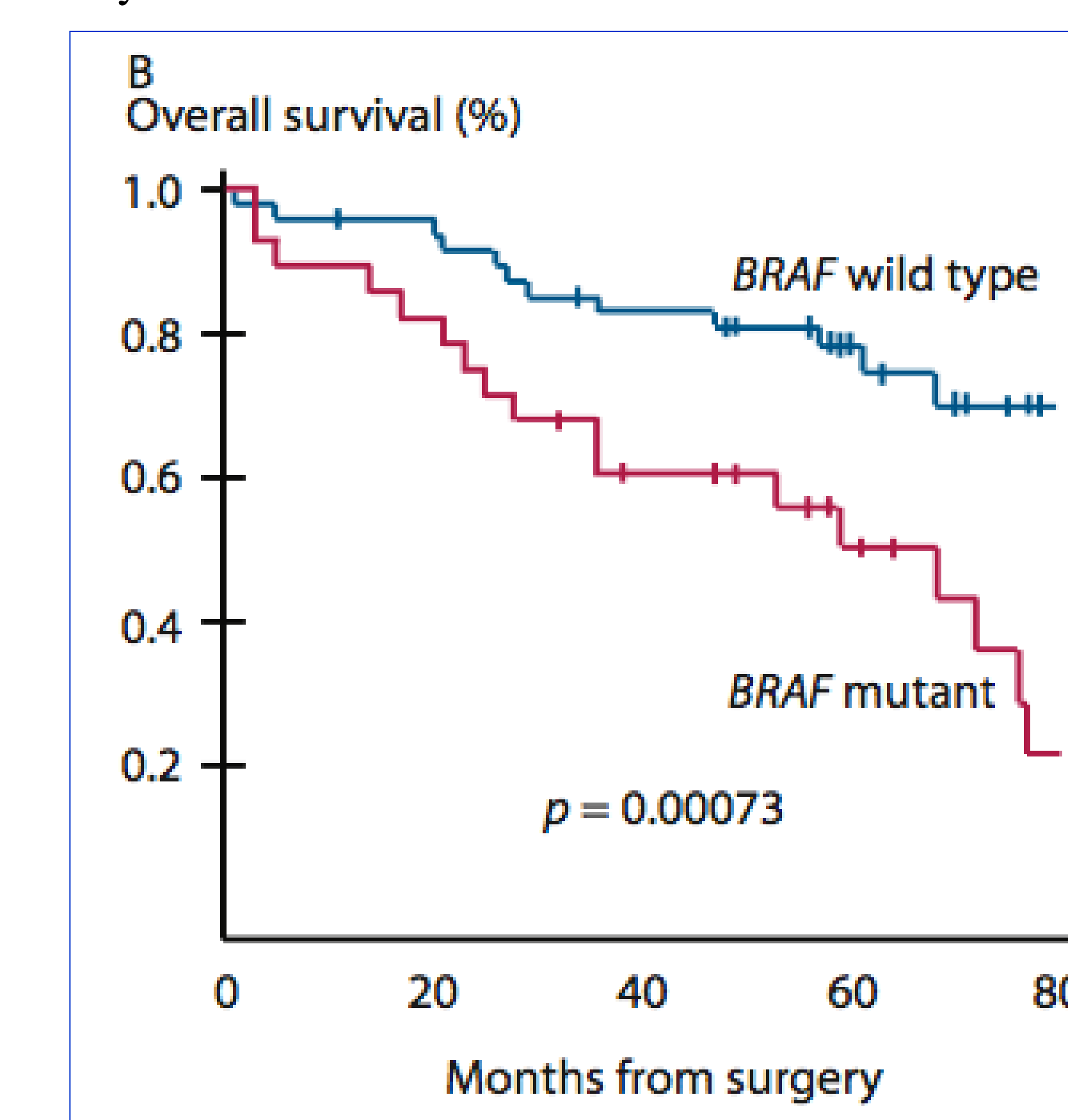
**Table 1. Categorization of patient tumors by BRAF mutation (Analysis population: 475).** Twelve percent of the study population study contained a BRAF mutation with a higher trend in females and older individuals. BRAF mutations were prominent within tumors of the proximal colon and associated with a moderate differentiation status and higher microsatellite instability.



**Figure 2A. Survival Kaplan-Meier curve comparison of patients containing BRAF wild-type or mutant microsatellite-stable tumors.** The patients containing microsatellite-stable mutant BRAF-expressing colorectal adenocarcinomas (RED) have a non-significant decrease in percent overall survival. Analysis based upon a 80 month interval following surgery from removal of colorectal adenocarcinoma tumor(s).



**Figure 1. Survival Kaplan-Meier curve comparison of patients containing BRAF wild-type or mutant stage I to III colorectal adenocarcinoma tumors (Analysis population: 322).** The patients containing mutant BRAF-expressing colorectal adenocarcinomas (RED) contained a statistically significant ( $p = 0.018$ ) decrease in percent overall survival. Analysis based upon a 120 month interval with a median follow-up analysis of 60 months.

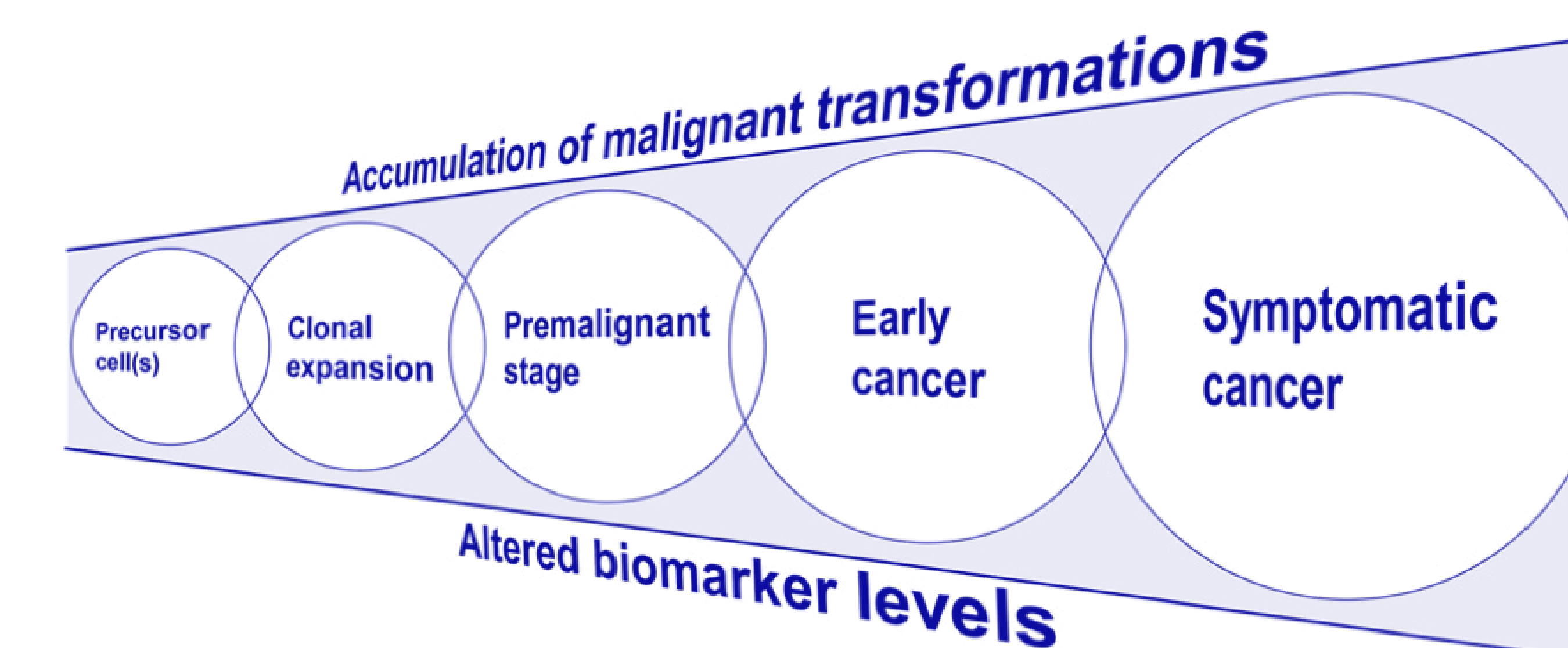


**Figure 2B. Survival Kaplan-Meier curve comparison of patients containing BRAF wild-type or mutant microsatellite-unstable tumors.** The patients containing microsatellite-unstable mutant BRAF-expressing colorectal adenocarcinomas (RED) have a statistically significant decrease in percent overall survival. Analysis based upon a 80 month interval following surgery from removal of colorectal adenocarcinoma tumor(s).

## Discussion:

Insight into the clinical effects and patient prognosis were determined based upon TTB of colorectal adenocarcinoma tissue samples that contained the biomarkers mutated BRAF and microsatellite instability. Results of these studies demonstrate that TTB colorectal adenocarcinoma tissue samples that contained mutated BRAF were more prominent in older individuals and females, exhibit high microsatellite instability, arise particularly in the proximal colon, and reduce overall survival. Since colorectal cancer may be resistant to chemotherapy and diminish patient prognosis, this information is absolutely essential in the development of therapeutics to eliminate mutated BRAF-expressing colorectal tumors in order to improve survival and prognosis of the patient. In other words, conventional 5-fluorouracil or EGFR-based therapies may not be effective in treating BRAF-expressing colorectal tumors and require a more specific therapy. This study recognizes the need for specific and personalized therapies based upon the characterization of a tumor tissue sample. TTB is advantageous for this approach by the allocation and classification of groups of tumor tissue samples by biomarkers that could be therapeutically targeted. In addition, this study highlighted the association of genomic instability, represented by increased microsatellite instability, in mutated BRAF-expressing colorectal adenocarcinoma tissue samples that elicited a worsened patient prognosis (4-5).

This study provides an example of how TTB is essential in translational medicine by identifying diagnostic and prognostic biomarkers of a disease, such as colorectal cancer. TTB permitted the study of colorectal adenocarcinoma tissue samples using the biotechnological applications of DNA purification, polymerase chain reaction, DNA sequencing, and microsatellite instability testing. As shown in the **schematic** below, tumorigenesis drives the cellular transformation of precursor cells into early and symptomatic cancer. The development of this process is attributed by the onset or change in levels of biomarkers that are crucial in diagnostic and prognostic determinations (1-2).



## Conclusion:

This study demonstrates that a series of biotechnological approaches can be used to characterize and identify diagnostic and prognostic biomarkers, which can be further investigated as therapeutic targets, from TTB samples. In the presented case, these biomarkers identified from TTB colorectal adenocarcinoma samples were mutated BRAF and microsatellite instability. This study captures the essence of TTB by the characterization of biomarkers that advance our understanding of the pathogenesis of a disease, such as colorectal cancer. This gives insight into strategizing, developing, or modifying therapeutics to prevent the onset and progression of diseases and may serve as a valuable branch of clinical oncology.

## References:

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