A Blood Test for Colorectal Cancer Detection using the mSEPT9 Biomarker

Catherine Loflin-Day, Theo deVos, Matthias Ebert, Jens Habermann, Robert Glucksman, Shannon Payne, Adhim Plumb
Epigenomics, Seattle, WA and Berlin, Germany – Technische Universität München – Hôpital für Chirurgie, Lubbeck – Technische Universität Dresden

Epigenomics’ Vision for Future CRC screening:

A simple blood test as part of the annual physical exam to indicate presence of CRC and to direct patients to colonoscopy

The CRC Screening Dilemma: Proven Benefit but Low Compliance

CRC Epidemiology
- Second leading cause of cancer deaths in the United States & Europe
- Third most common cancer diagnosed in men and women
- Accounts for ~10% of total cancer burden
- Lifetime risk is ~6%
- 5-Year survival ~90% when diagnosed at Stage I but ~10% when diagnosed at Stage IV

CRC Screening
- CRC lends itself to population screening:
  - Common disease with severe consequences
  - Relatively well defined natural history
  - Can be detected at an early stage
  - Diagnostic tests & effective treatments are established
- Evidence demonstrates a reduction of mortality associated with early detection of disease through CRC screening

CRC screening Compliance
- Guidelines in the U.S. and Germany recommend Screening by FOBT, Colonoscopy and other methods
- Despite numerous CRC screening options, patient adherence remains low
- The majority of the eligible U.S. population is currently not screened according to CRC screening guidelines
- As a consequence, the majority of CRC cases are currently diagnosed in advanced stages
- American Cancer Society goal: Increase Colorectal Cancer Screening Compliance to 75% by 2015

DNA Methylation Biomarkers for Cancer Detection in Blood

DNA methylations are modifications of DNA that occur naturally in the cell. They play a critical role in gene regulation and are often altered in cancer cells. Identifying these modified DNA molecules in peripheral blood can provide a non-invasive method for detecting cancer.

\[\text{DNA Methylation Pattern} \xrightarrow{\text{Detection}} \text{DNA Methyltransferase} \xrightarrow{\text{Real-time PCR}} \text{Result}\]

References

**SEPT9: A CRC Biomarker in Blood Identified and Validated in Systematic Approach**

1. Identification of mSEPT9 as candidate DNA methylation biomarker for CRC in tissue through genome-wide screening
2. Characterization of mSEPT9 biomarker in tissue
   - Sensitivity for CRC
   - Specificity for CRC vs. other cancers, other disease and healthy tissues
3. Development of sensitive real-time PCR assays
4. Verification of biomarker assay performance in plasma
   - Sensitivity for CRC
   - Specificity for CRC vs. other cancers, other diseased healthy controls
5. Development of highly sensitive assay procedure for clinical laboratory use
6. In Progress: Demonstration of mSEPT9 performance in CRC screening population (PRESEPT Study)

**SEPT9 is Methylated in the Vast Majority of CRC Tumors**

- Epigenetics identified SEPT9 as a gene methylated in over 90% of CRC tumors
- Complex gene locus with multiple promoters and alternatively spliced exons
- Member of Septin family, a conserved family of GTP-binding proteins
  - Identified as cdc mutations in yeast (Hartwell, Culotti, and Reid. 1970. PNAS. 66: 352-359.)
  - Involved in diverse cellular processes
- SEPT9 identified in a region of allelic imbalance in breast and ovarian cancer
- SEPT9 is fusion partner of the proto-oncogene MLL
- Altered RNA expression of SEPT9 found in many malignancies
- DNA methylation changes identified by Epigenomics are highly specific for colorectal cancer

**SEPT9: Consistent Marker Performance in Blood**

- When measured in blood, methylated DNA methylation pattern of the SEPT9 gene reliably indicated the presence of CRC in seven case-control studies with over 3000 subjects in total
- The current SEPT9 assay detects CRC (Stages I-IV) with a sensitivity of ~70% at a specificity of ~90%.

**SEPT9 Assay for Routine Testing**

- Epigenomics’ mSEPT9 assay is already FDA approved for routine testing.
- The assay is based on real-time PCR technology.

**Outlook**

- Epigenomics’ partner Abbott is expected to launch a CE-marked mSEPT9 on the m2000 platform in Europe in late 2009, FDA submission for the US is expected for 2010.
- Quest Diagnostics is expected to launch a laboratory developed test in the US in due course.
- Several European laboratories are in the process of establishing and validating mSEPT9 assays based on Epigenomics’ mSEPT9 research product for sale in Europe.
- The ongoing prospective PRESEPT Study with results expected in late 2009 will demonstrate mSEPT9 performance in a screening population.