Blood-based screening tests for colorectal cancer: Where are we and where are we going?

Timothy R. Church
Division of Environmental Health Sciences
University of Minnesota School of Public Health
Background

CRC screening tests are effective, but not popular
In 2012, 65.1% of U.S. adults were up-to-date with CRC screening, and 27.7% had never been screened\(^1\) (2012)
A non-invasive blood test, with appropriate sensitivity and specificity, would be useful
The septin9 (Epi proColon) test presented today represents the first widely available one, but others are not far behind

\(^1\)MMWR, November 8, 2013 / 62(44);881-888, http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6244a4.htm
Threads

- There are three main threads that will interweave to improve the ability to screen with blood tests
  - Identifying new individual markers that are associated with the presence of neoplasia or risk of developing cancer
  - Increasing knowledge of the normal-mucosa→adenocarcinoma sequence
  - Refining of laboratory methods to identify lower levels of circulating molecules
Identifying individual markers

• In addition to the three markers discussed today, there are others currently in development.

• Finding, evaluating, and validating new biomarkers requires access to representative cases and controls.

• Recruiting, collecting specimens from, and endoscopically examining subjects for each phase of each new biomarker candidate is prohibitively costly.

• Need to create accessible, large, well characterized biorepositories.
Examples of existing biorepositories

- **EDRN’s GLNE010**
  - Initial target: recruitment of >8000 pre-colonoscopy subjects
  - Want at least 70 CRC/high-grade dysplasia cases
  - Specimens: whole stool, blood, urine
  - Current status: seeking additional funding to complete recruitment and collection

- **PLCO**
  - 155,000 men and women
  - Up to 75,000 with 1-6 samples of blood
  - Screen-detected colorectal cancer
  - Current status: available for validation of well-characterized biomarkers
Increasing knowledge of the normal-mucosa→adenocarcinoma sequence

• Potential markers
  – Germline genetic susceptibility markers
  – Methylation status of WBC
  – Circulating somatic DNA mutations
  – Circulating methylated DNA (SEPT9, vimentin)
  – Circulating RNA (microRNA panels)
  – Circulating proteins & post-translation mods
  – Immune marker panels, etc.

• How do they all fit together?
  – Simple additive brute force models?
  – Direct modeling of known biology?
  – Better causal models → better prediction?
Refining of laboratory methods to identify lower levels of circulating molecules

- Refinement of old methods
  - Increasing sensitivity of mass spectrometry
  - PCR-based device improvements
- New methods
  - Nanoparticle/nanotube/nanopore probes
  - Antibody-magnetic particle complex
- As methods improve, lower levels/smaller samples and more precise quantification will result, widening potential biomarker domain
Weaving the threads together

• Biomarkers are not competitors but collaborators
• Initial attempts at combining them have been crude and not that successful, e.g., stool DNA
• Better understanding of the carcinogenesis process will lead to
  – better search methods for new markers, and
  – better models for combining markers based on actual biological processes, incorporating
    – Threshold functions
    – Continuous linear and non-linear parameterized functions, and
  – Biologically determined interactions
Combining biomarkers: dichotomous vs. continuous?
Distribution of Predictor 1 by group
Distribution of Predictor 2 by group
Multivariate prediction

• Assume Predictor 1 and Predictor 2 have correlation of 0.80 within groups
• Plot members of two risk groups by two predictors
Discriminating on 2 predictions
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