

Putting Knowledge into Practice: First Transatlantic Symposium on Strategies to Increase Colorectal Cancer Screening and Save More Lives

PRESEPT Initiative: Evaluation of the Clinical Performance and Health Economic Benefits of the Blood-Based ^mSEPT9 Biomarker for Colorectal Cancer Detection

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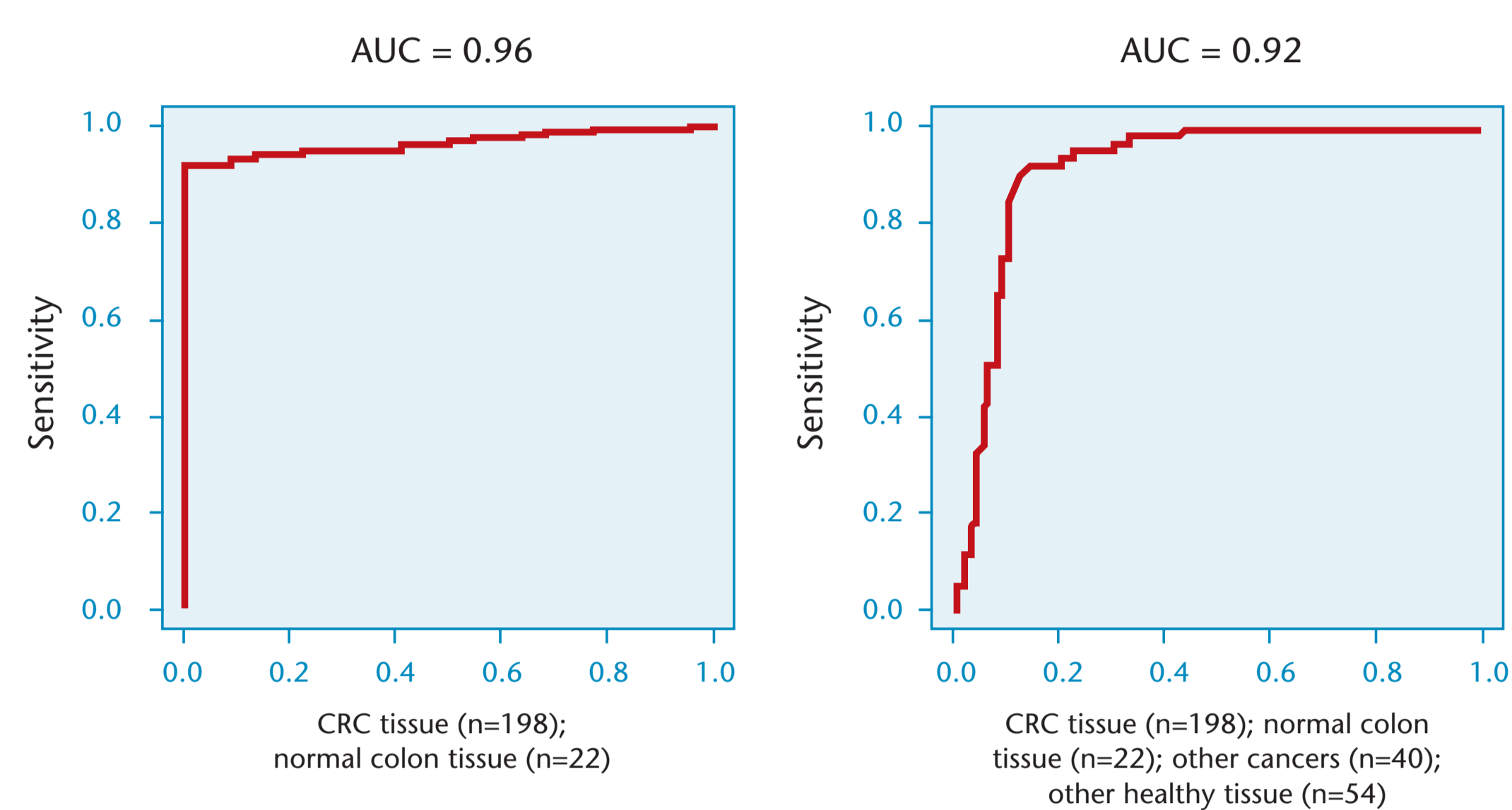
Background

Colorectal cancer (CRC) is the second leading cause of cancer related death with an estimated direct medical treatment costs of \$8.4 billion in the U.S. in 2007. With a cure rate over 90% if diagnosed in early stages, guidelines recommend that average-risk adults aged 50 and older should be screened for colorectal cancer.

However, the majority of the U.S. guideline eligible screening population have not had a recent test. Thus, poor adoption of currently available screening options limits the effectiveness of CRC screening initiatives.

Epigenomics discovery efforts yielded a molecular diagnostic marker, ^mSEPT9, methylated in more than 90% of the CRC tissue tested on a proprietary methylation microarray.

In 2005–2008 several subsequent case-control studies, analyzing plasma obtained from more than 3000 colonoscopy verified subjects, demonstrated methylation of the SEPT9 gene is highly associated with the presence of colorectal cancer.



Patient Group	Case Control Training Study 2008 (N=269)**			Case Control Testing Study 2008 (N=249)**		
	Positive/ Tested	% Positive	C.I.	Positive/ Tested	% Positive	C.I.
Stage I	10/22	45	[24,68]	10/20	50	[27,73]
Stage II	31/37	84	[68,94]	29/40	72	[56,85]
Stage III	28/35	80	[63,92]	20/27	74	[54,98]
Stage IV	3/3	100	[29,100]	4/4	100	[40,100]
Stage I-III	69/94	73	[63,82]	59/87	68	[57,78]
Stage I-IV	72/97	74	[64,83]	63/91	69	[59,78]
Controls	13/172	8	[4,13]	17/158	1	[6,17]

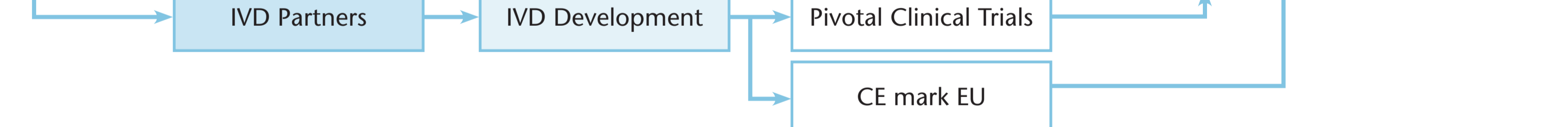
The PRESEPT Initiative

Objectives

- Establish SEPT9 performance characteristics in an average to increased risk cohort in an international multi-center, prospective study in the USA and Germany
- Obtain FDA agreement for clinical plan supporting IVD PMA approval based on samples and clinical data obtained under ICH GCP controls
- Demonstrate health economic benefit to support national healthcare and private insurer coverage
- Obtain medical community acceptance of SEPT9 assay for CRC screening and gain inclusion into multi-societal screening guidelines

Methods

- Establish top tier Medical Advisory Board (MAB) to guide the process
- Conduct a cost-effective, prospective multinational study in the U.S. and Germany in full compliance to ICH GCP and human studies regulations
- Design well validated Markov Model using prospective study performance data to support health economic analysis
- Assure regulatory compliance and best clinical practices via oversight by an expert Clinical Study Steering Committee and www.clinicaltrials.gov registration



Colorectal Cancer Medical Advisory Board

Douglas Rex, MD – Chancellor's Professor and Professor of Medicine at Indiana University School of Medicine
Philip Schoenfeld, MD, M.Ed., M.Sc. – Associate Professor, Department of Internal Medicine, Director, Training Program in GI Epidemiology University of Michigan
Richard Wender, MD – Alumni Professor and Chairman of the Department of Family Medicine at Thomas Jefferson University in Philadelphia
Deborah Fisher, MD, MHS – Assistant Professor of Medicine, Duke University
Scott Ramsey, MD, PhD. – Associate Professor of Medicine and Health Services, Director of Cancer Outcomes Research at the Fred Hutchinson Cancer Center

PRESEPT Study Design

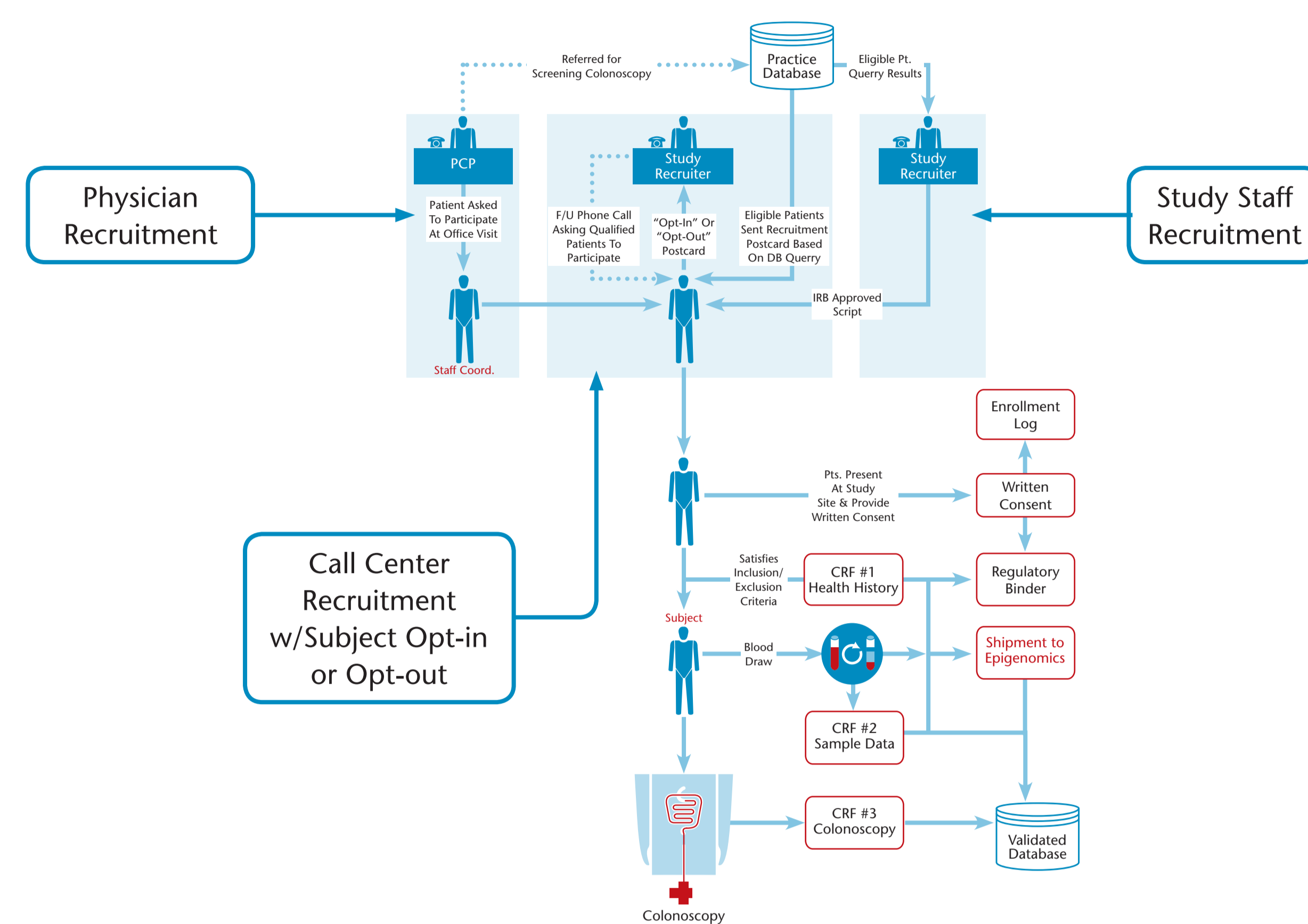
- Study Population & Cohort Characteristics
- CRC screening guideline-eligible subjects, i.e.
 - Asymptomatic individuals at average to increased risk for CRC
 - 50 years of age or older
- Collection of 40ml blood & health data collected from each subject
- Accrual of 7500 subjects expected to identify 50 CRC cases
- 22 clinical sites in the U.S. and Germany
- Age and gender accrual targets to reflect target population

PRESEPT Study Endpoints

Primary Endpoint: Clinical/surgical diagnosis of invasive colorectal adenocarcinoma detected by optical colonoscopy and confirmed by histology compared to the ^mSEPT9 Biomarker classification.

Secondary Endpoint: Detection of polyp(s) equal to or greater than 10mm, flat lesion(s), or non-invasive adenocarcinoma (CIS) by colonoscopy and confirmed by histology compared to the ^mSEPT9 Biomarker classification will also be described.

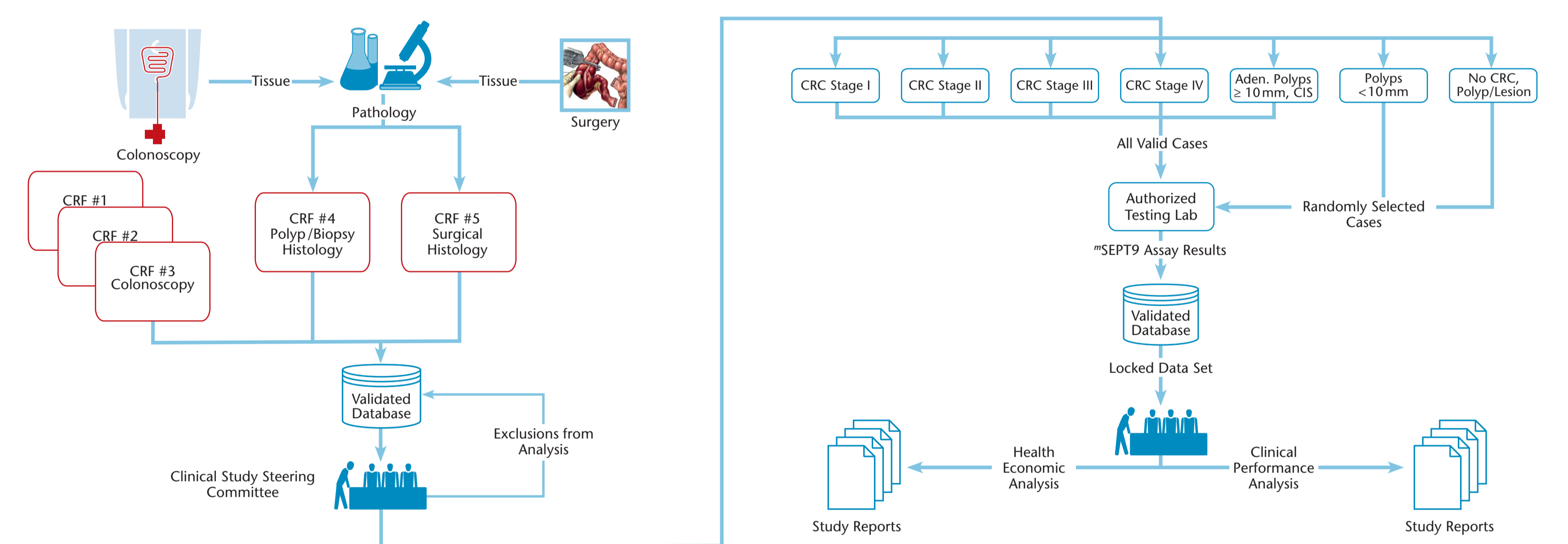
PRESEPT Study Flow – Recruitment to Colonoscopy



PRESEPT Study Inclusion / Exclusion Criteria

- Qualifications**
- 50 years of age scheduled for colonoscopy for CRC screening
 - Capable of providing informed consent & health history
- Inclusion Criteria**
- Age 50 or older at time of colonoscopy
 - Accessible for blood draw prior to start of bowel prep
 - First large bowel colonoscopy in lifetime
- Exclusion Criteria**
- Hematochezia in prior 6 mo. for which patient received or sought medical attention
 - Iron deficiency anemia in prior 6 mo. for which patient received medical attention
 - Familial high risk for colorectal cancer

PRESEPT Study Design – Data Capture and Analysis



PRESEPT Study Clinical Study Steering Committee

The PRESEPT Clinical Study Steering Committee advises on study design, oversees study conduct, and will independently analyze and accurately report the study results. The CSSC membership composition:

David Ransohoff, MD – Professor of Medicine, Cancer Epidemiology, Cancer Prevention and Control, University of North Carolina School of Medicine, CSSC Chair
Neal Osborn, MD – Co-Director of Clinical Research, Atlanta Gastroenterology
Timothy Church, PhD – Professor, School of Public Health, University of Minnesota
Brent Blumenstein, PhD – Principal, Trial Architecture Consulting
Dale Snover, MD – Adjunct Professor, Department of Laboratory Medicine and Pathology, University of Minnesota Medical School
Prof. Thomas Rösch, MD – Director of the Department of Interdisciplinary Endoscopy University Hospital Hamburg-Eppendorf, Germany
Robert Day, MD, PhD – President Emeritus of The Fred Hutchinson Cancer Research Center (ex officio member)
Michael Wandell, PharmD – Study Director, Epigenomics
Cathy Lofton-Day, PhD – Project Manager, Epigenomics

Health Economic Evaluation

- Validated Markov Model developed by Uri Ladebaum, MD, UCSF, San Francisco, CA
- Compares consequences and cost-effectiveness of CRC ^mSEPT9 blood-based screening compared to current screening alternatives for average-risk individuals
- Cohort Simulation: Average quality adjusted life-years saved and cost per person
- Design: Cost effectiveness analysis from a societal viewpoint
- Outcome Measures: Discounted lifetime costs, life expectancy, and incremental cost-effectiveness ratios
- Analysis will account for screening uptake & adherence

Adherence Study

A study design is in preparation to demonstrate 'uptake' as a key determinate of increasing CRC screening in the average risk population

Study design in planning and considering a 'Consumer Intercept', 'Complier and Non-Complier Questionnaire', and 'Available Choice Selection Models'

Summary

The PRESEPT Initiative is comprised of several key activities addressing medical and societal issues influencing the adoption of a new, blood-based CRC screening method. Through this initiative and the PRESEPT Study, Epigenomics will characterize the ^mSEPT9 biomarker clinical performance characteristics, the health economic benefits of, and improved adherence to, a minimally invasive, blood-based CRC screening method in its intended use population. It is believed that a convenient, minimally invasive test will significantly increase the number of average risk patients screened.