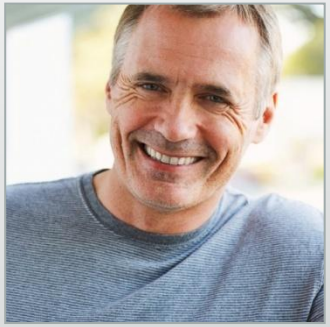
Institute of Medicine
Washington DC
May24, 2012






finding cancer early
epigenomics

Advancing the Utility of Oncology Diagnostics: IVD Perspective

Patient

Healthcare Providers

Colorectal Cancer

Payers

Clinical Laboratories

CRC Screening Guidelines

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Topics

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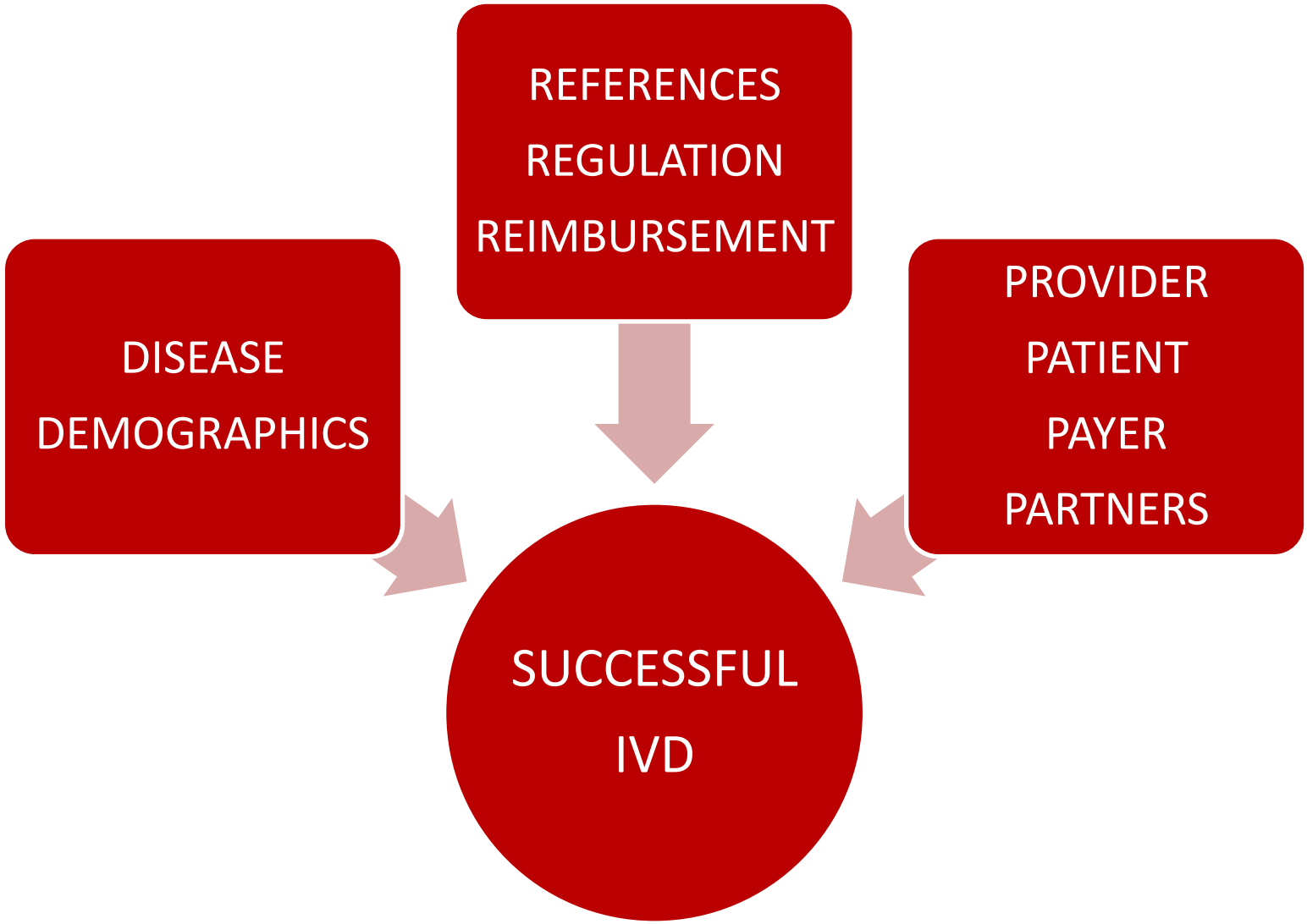
2D3R4P MODEL FOR IN-VITRO DIAGNOSTICS



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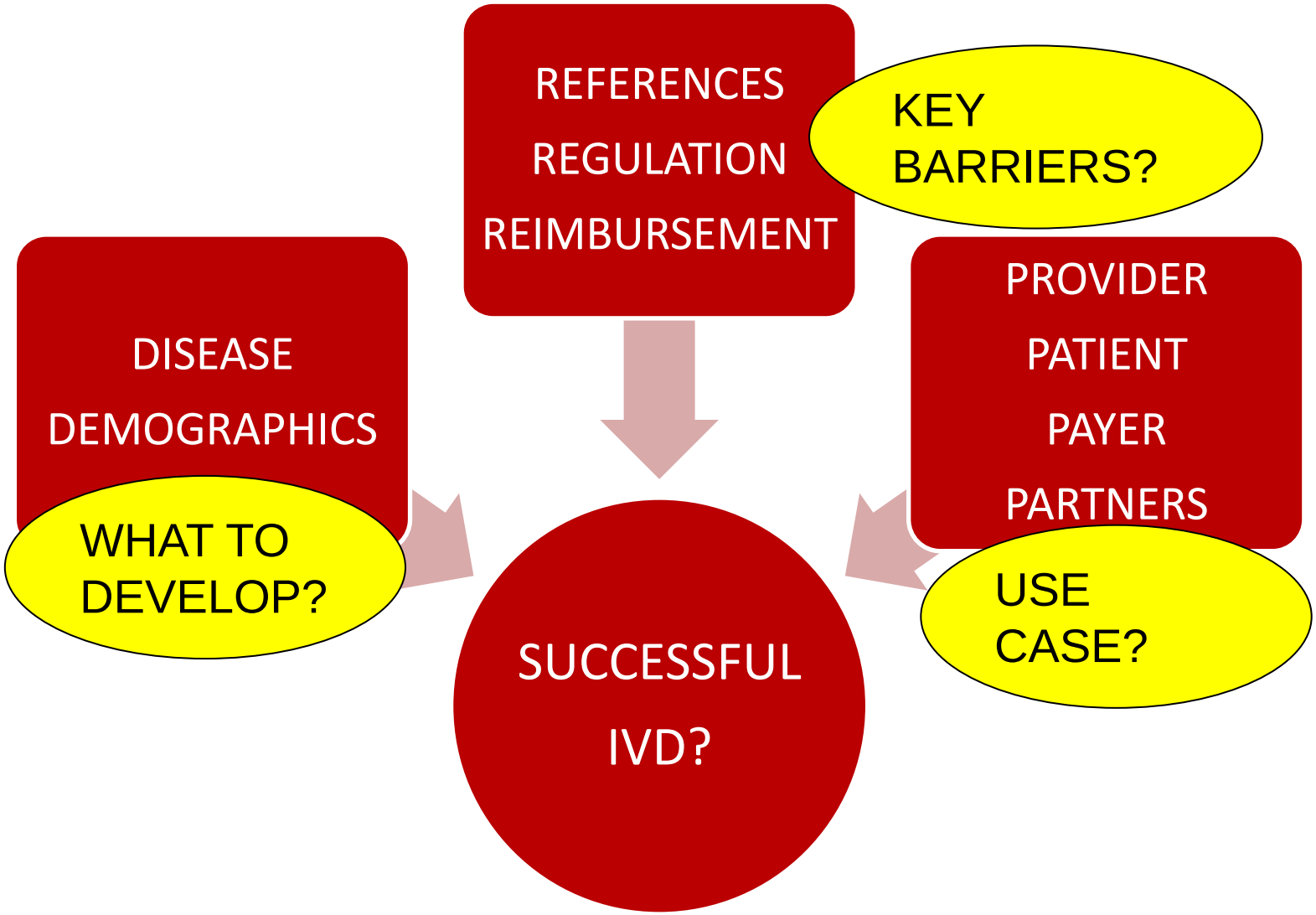
2D3R4P MODEL…….ELEMENTS REQUIRED FOR SUCCESS



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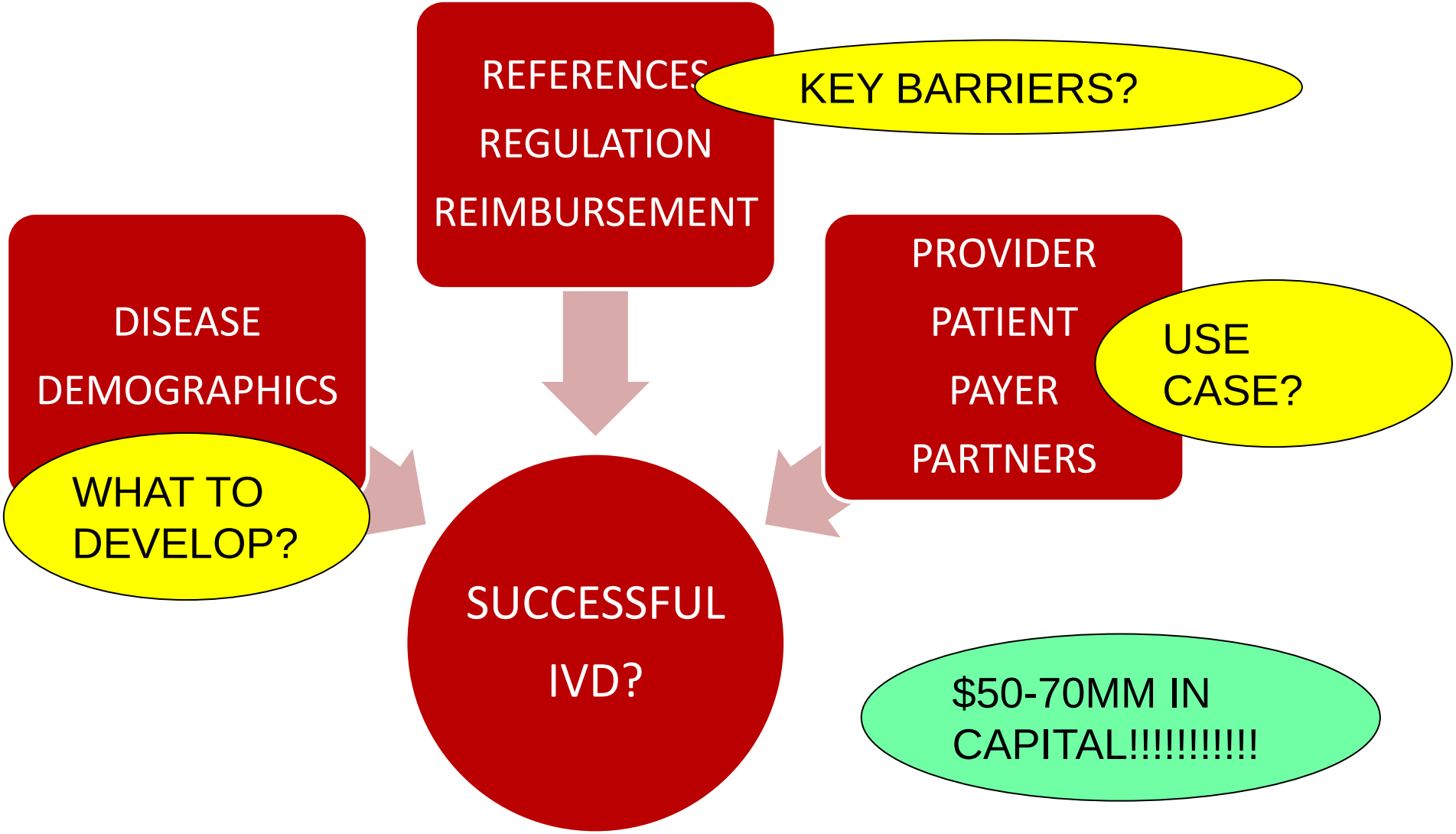

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Medicine is Business!

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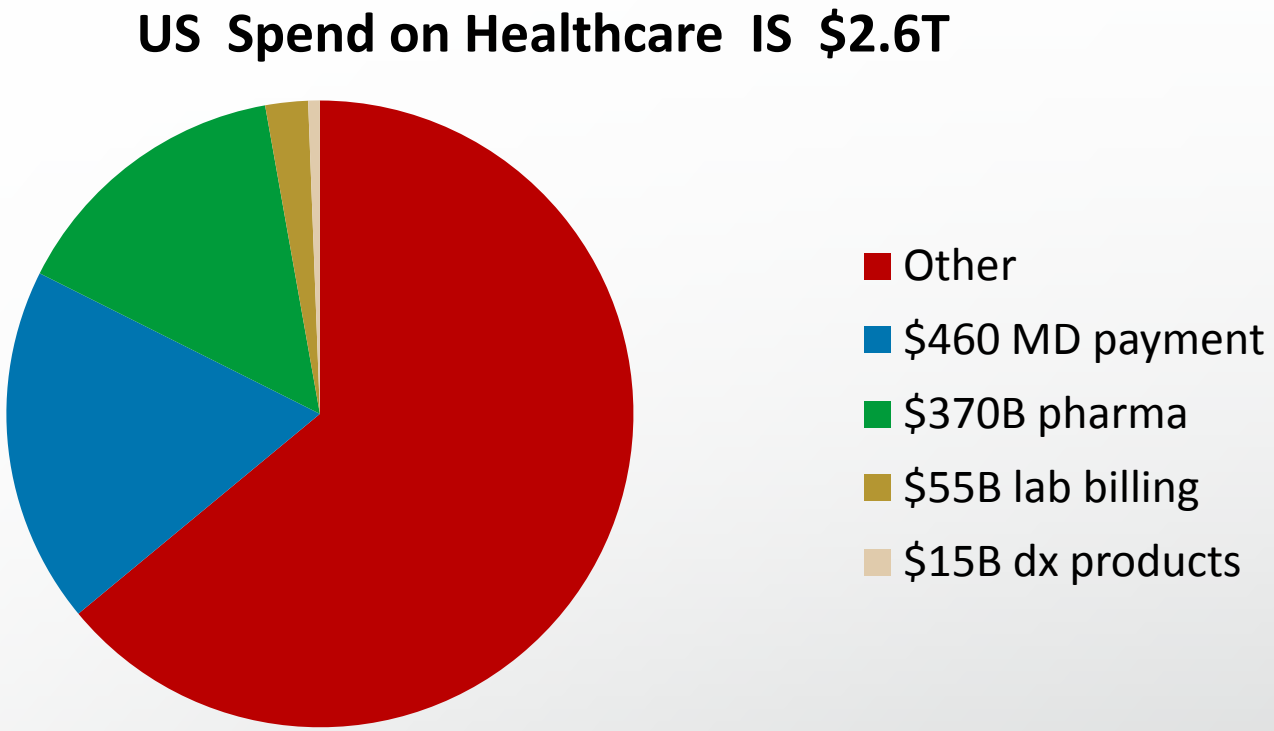
DISCONNECT BETWEEN DX VALUE AND IMPACT



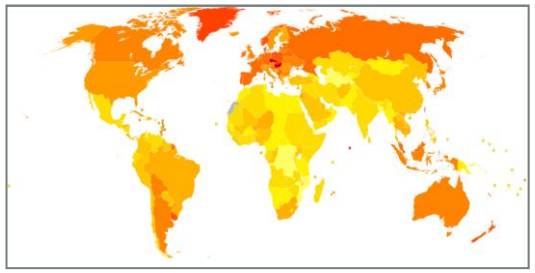
Lewin Study: ~3/4 of all decisions based on Dx result……a real bargain?

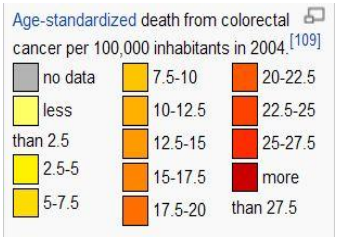
Observation: The IVD industry is LOUSY at documenting and sharing success!

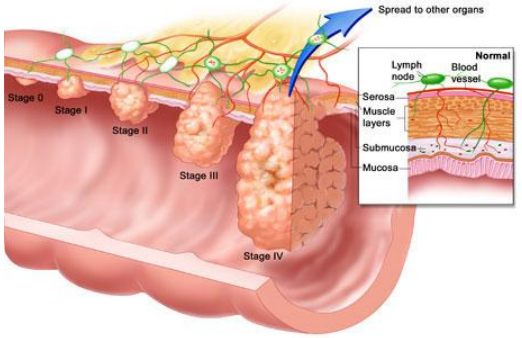
Examples: TDMs, Lipids, MI, heart failure, POC ID, Leukemia, HIV, etc.

Colorectal Cancer (CRC) Screening Saves Lives….

- CRC is the second largest cancer killer: ***~140.000 new cases*** and ***~50.000 deaths***[1] each year in the US
- Disease of the developed world: Highest prevalence in North America and Europe (***15-20 deaths per 100.000 inhabitants***[2])
- CRC ***is curable*** if detected early enough!
- ***5-year survival*** for diagnosed and treated Stage I/II CRC: ***90%***
- CRC screening has proven to ***reduce mortality***







	5-year survival[3]
with screening	**73%**
without screening	46%

1) American Cancer Society.: Cancer Facts and Figures 2012. Atlanta, Ga: American Cancer Society, 2012. 2) http://en.wikipedia.org/wiki/Colorectal_cancer
3) Survival rate for colorectal cancer by stage. Source: National Cancer Institute, PDQ, Treatment, Health Professionals ww.meds.com/pdq/colon_pro.html

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CRC Screening Saves Money

US$ 17+ billion

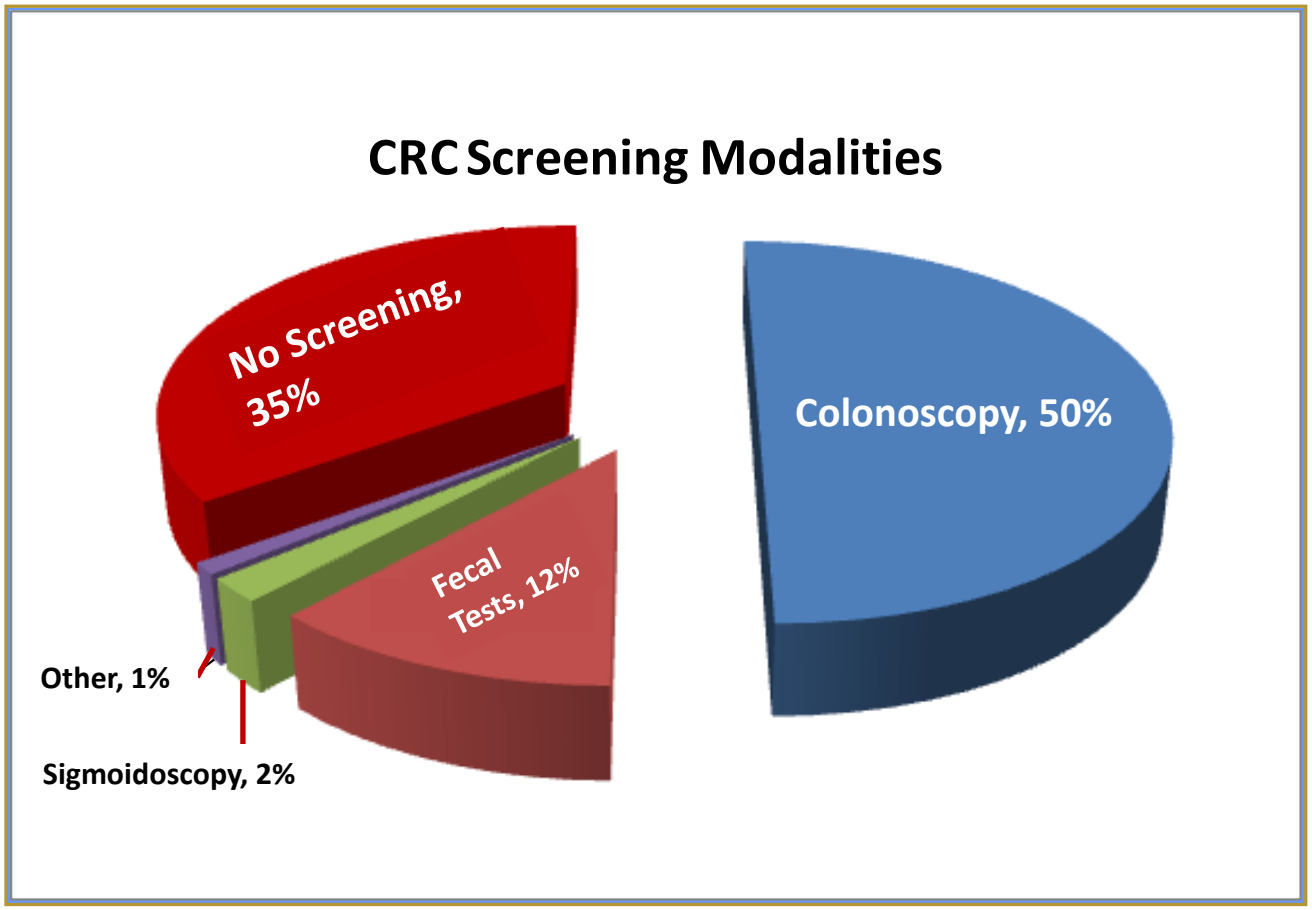
total colorectal cancer related annual costs incurred in the U.S.

($7B initial year, $5B continuing care, $5B last year)

Key Challenge: non-compliance to existing
stool-based or invasive (colonoscopy) CRC screening options

Centers for Disease Control. "Vital signs: Colorectal cancer screening, incidence, and mortality---United States, 2002-2010. " MMWR Morb. Mortal. Weekly Report. 2011, 60(26):884-889

US Market Target……A New Awareness Is Emerging



- 1 of every 3 age-eligible, still not screened
- The gold standard is not the perfect standard! R/L, operator variability
- Stool-based methods are in decline

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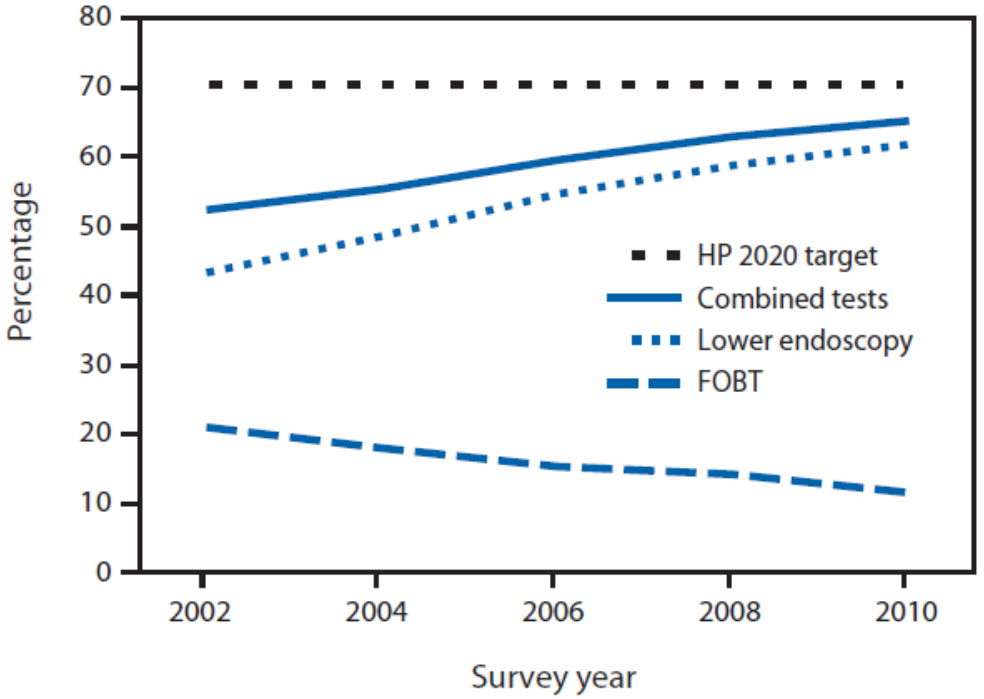
Trends in CRC Screening

FIGURE 1. Percentage of respondents aged 50–75 years who reported receiving a fecal occult blood test (FOBT) within 1 year and/or a lower endoscopy* within 10 years and *Healthy People 2020* (HP 2020) target — Behavioral Risk Factor Surveillance System (BRFSS) surveys, United States, 2002, 2004, 2006, 2008, and 2010†



* Sigmoidoscopy or colonoscopy.
† Age-standardized to the population aged 50–75 years in the 2010 BRFSS survey.

MMWR – July 8, 2011 : 60(26):887

- Gains in screening compliance based on colonoscopy. But reimbursement changes coming in 2015.
- Stool-based methods show continuous decline despite excellent pricing and improved test performance - FIT

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The Issue: USPSTF

- **Underuse of Screening**
- Colorectal cancer screening remains underused, despite the availability of effective screening tests.
- Screening for colorectal cancer lags far behind screening for breast and cervical cancers.
- Findings from the National Health Interview Survey (NHIS), which is administered by CDC, indicate that in 2005, only 50% of U.S. adults age 50 or older had undergone a sigmoidoscopy or colonoscopy within the previous 10 years or had used a fecal occult blood test (FOBT) home test kit within the preceding year.
- Screening for colorectal cancer was particularly low among those respondents who lacked health insurance, those with no usual source of health care, and those who reported no doctor's visits within the preceding year.
- As many as 60% of deaths from colorectal cancer could be prevented if everyone age 50 and older were screened regularly.

Closing the Gap in Colon Cancer Screening: Preference Survey

- Study Details
  - Two telephone surveys conducted among 1,304 adults of 614 men/690 women ≥ 50 years of age
  - Questions pertained to the respondents' knowledge and experience with colon cancer screening
- Summary of Highlights and Conclusions
  - Nearly 1 of 3 or 31% (≥ 50 years) have never been screened for CRC
  - Of the respondents that had been screened, colonoscopy was the primary method employed
  - Healthcare providers are the key influencer for CRC screening
    - Healthcare providers have the opportunity to both educate patients on the value of screening and correct misinformation

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Closing the Gap in Colon Cancer Screening: Preference Survey

- Major impediments to screening:
  - Unpleasantness associated with stool tests
  - Time constraints, risks/fears associated with colonoscopy prep and anesthesia
  - Unreimbursed costs
  - Patients are often lulled into a false sense of security after one colonoscopy and fail to undergo subsequent testing
  - The availability of a blood test may promote higher rates of screening by providing opportunity to evaluate patients who otherwise would never be screened, and – *in this survey*:
    - 80% would forego a modern convenience if they could initially be screened via a blood test versus a colonoscopy (wine, chocolate or a cell phone for 6 months)
    - 78% likely to take a blood test for colon cancer screening
    - 75% were more likely to get screened more frequently if a blood test were available

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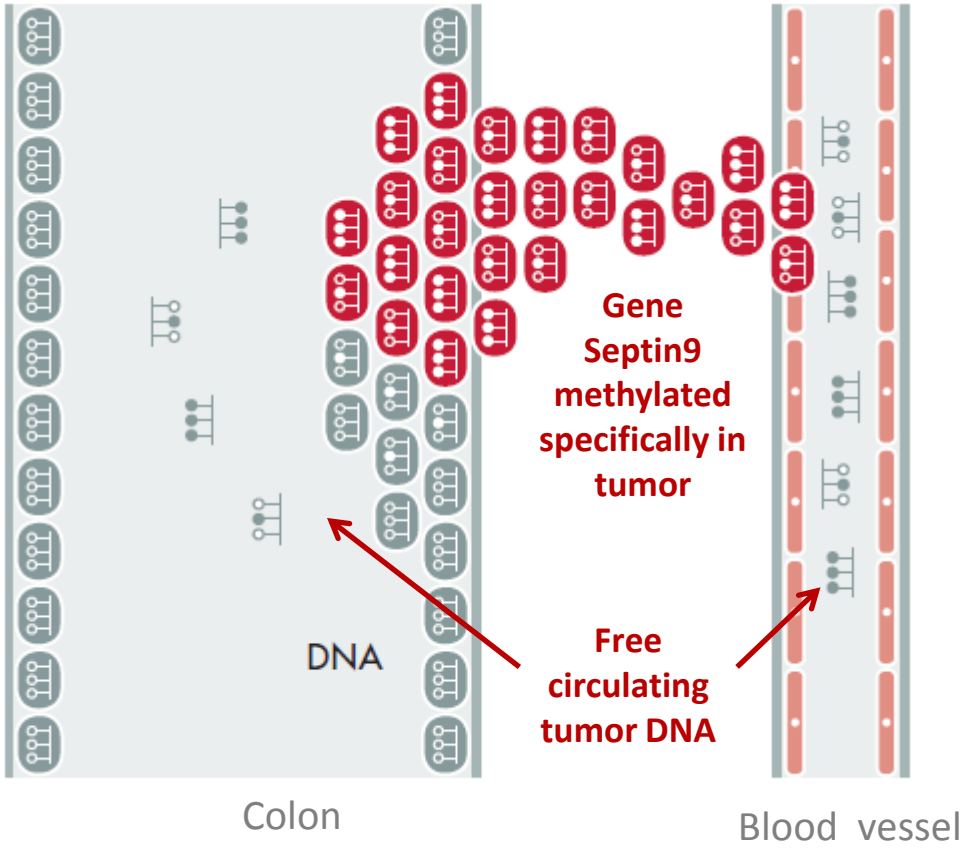
Septin9 Test for CRC Screening

- Proprietary Biomarker:
  methylated Septin9 gene
- Detection of free circulating tumor DNA in blood by established ***real-time PCR*** test down to
  6 pg / ml methylated Septin9
- Strong ***patent position***: biomarkers, technology, processes
- 13 published retrospective clinical studies performed:
  >4,300 subjects tested
- ***Prospective clinical screening study*** recently completed
- New CPT code **81401** announced !



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Epi proColon, Second—Gen Product

- Epi proColon, description and workflow
- Proposed Intended Use
- Indications for Use
- FDA PMA Modular Process
- PMA Filing Status

- Fast results available in ~ 8 hours
- Real-time PCR-based assay on FDA cleared AB7500 Fast Dx instrument
- Compliance
  - cGMP manufactured, 21 CFR Part 820
  - ISO 13485 compliant

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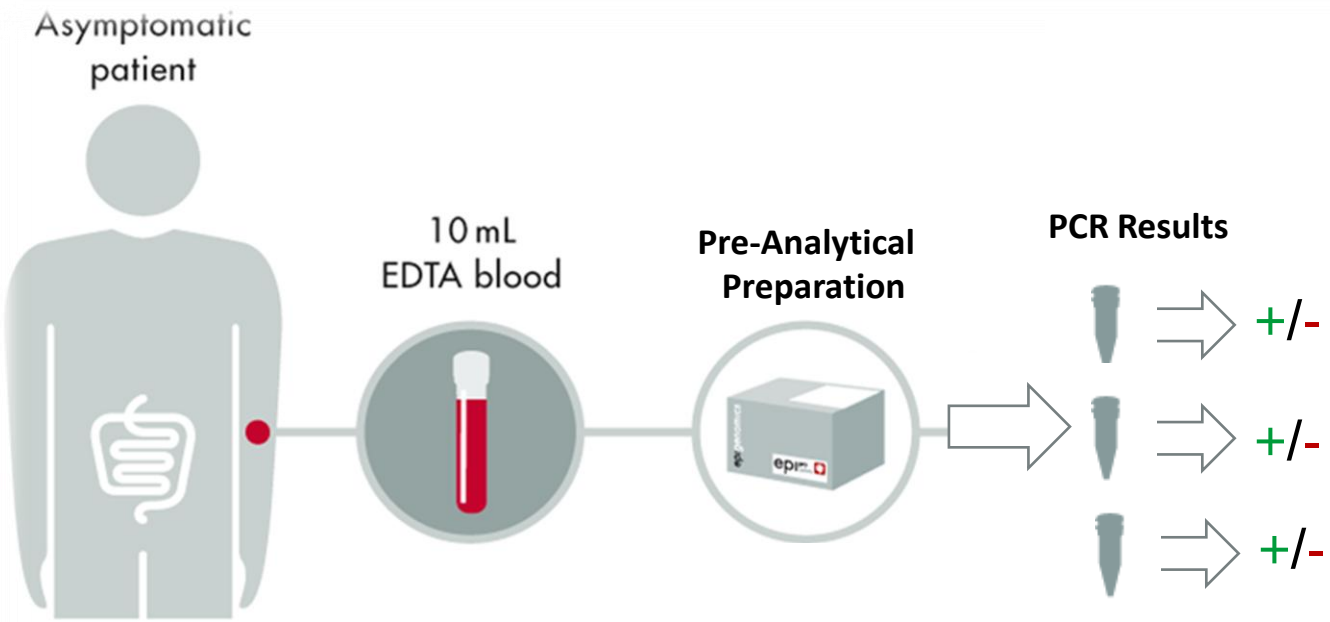
Epi proColon® “2.0” Workflow



Minimum of 1 PCR Positive
=> Positive Test

Optimized for Sensitivity
Allowing the highest possible number of CRC cases detected!

one assay. one marker. simple qualitative interpretation

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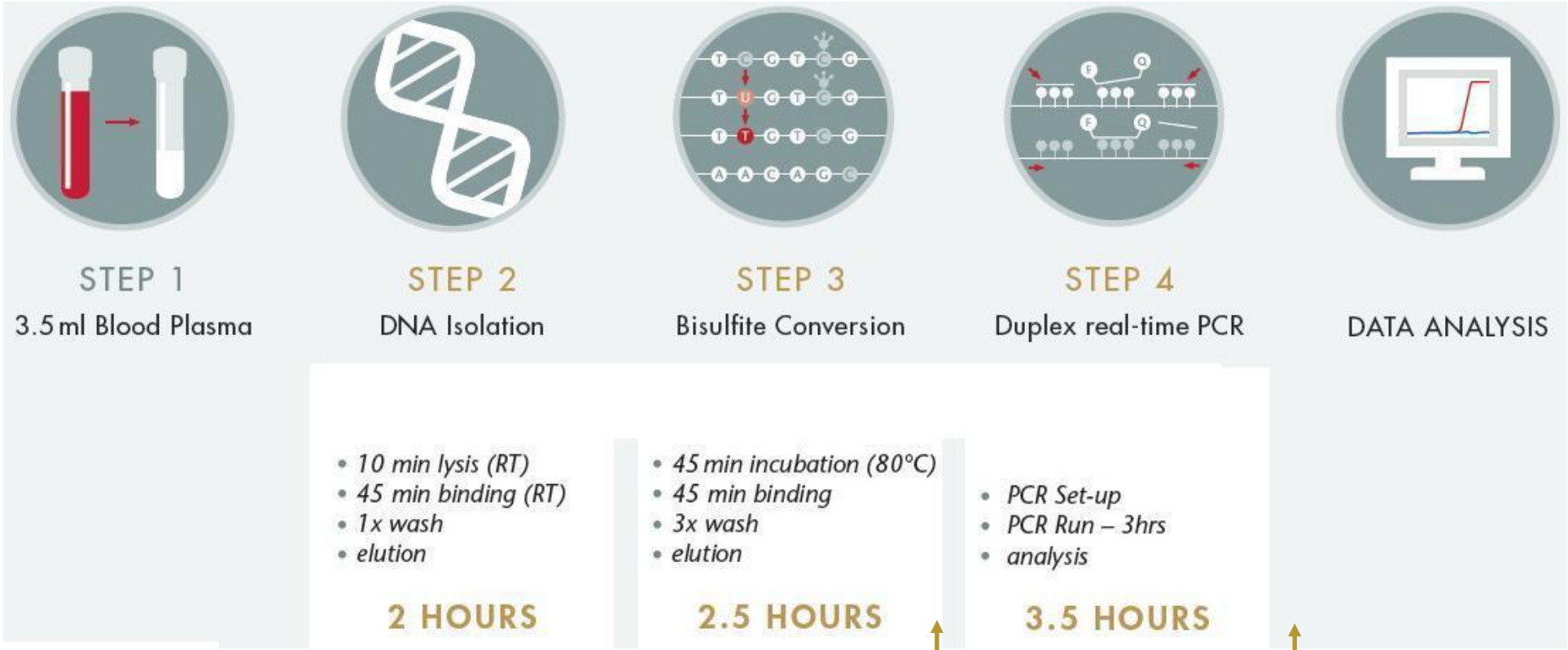
Epi proColon: A Single “Shift” Assay For Colorectal Cancer



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Proposed Intended Use

Intended Use

Epi proColon is a qualitative assay for the real-time PCR detection of methylated Septin9 DNA in EDTA plasma.

Epi proColon is an aid in screening patients defined as average risk for colorectal cancer by current screening guidelines.*

*Intended use has been accepted by FDA pending review of submission.

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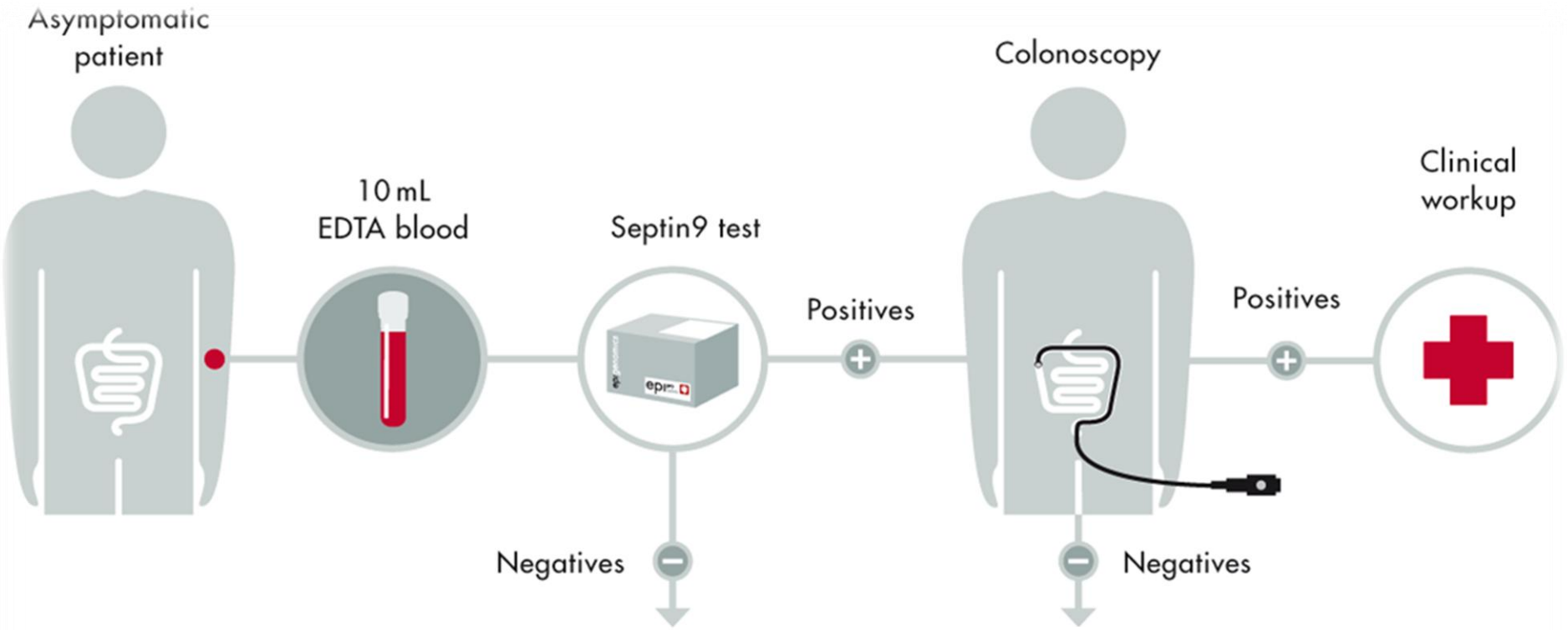
Clinical Application of Septin9 Tests in CRC Screening



Repeat blood test conducted at intervals consistent with practice guidelines and other non-invasive CRC screening tests, e.g. annually.

Colonoscopy according to guidelines
next CRC screening colonoscopy to be performed according to guidelines, e.g. 10 years later
Appropriate repeat blood test interval frequency according to practice guidelines

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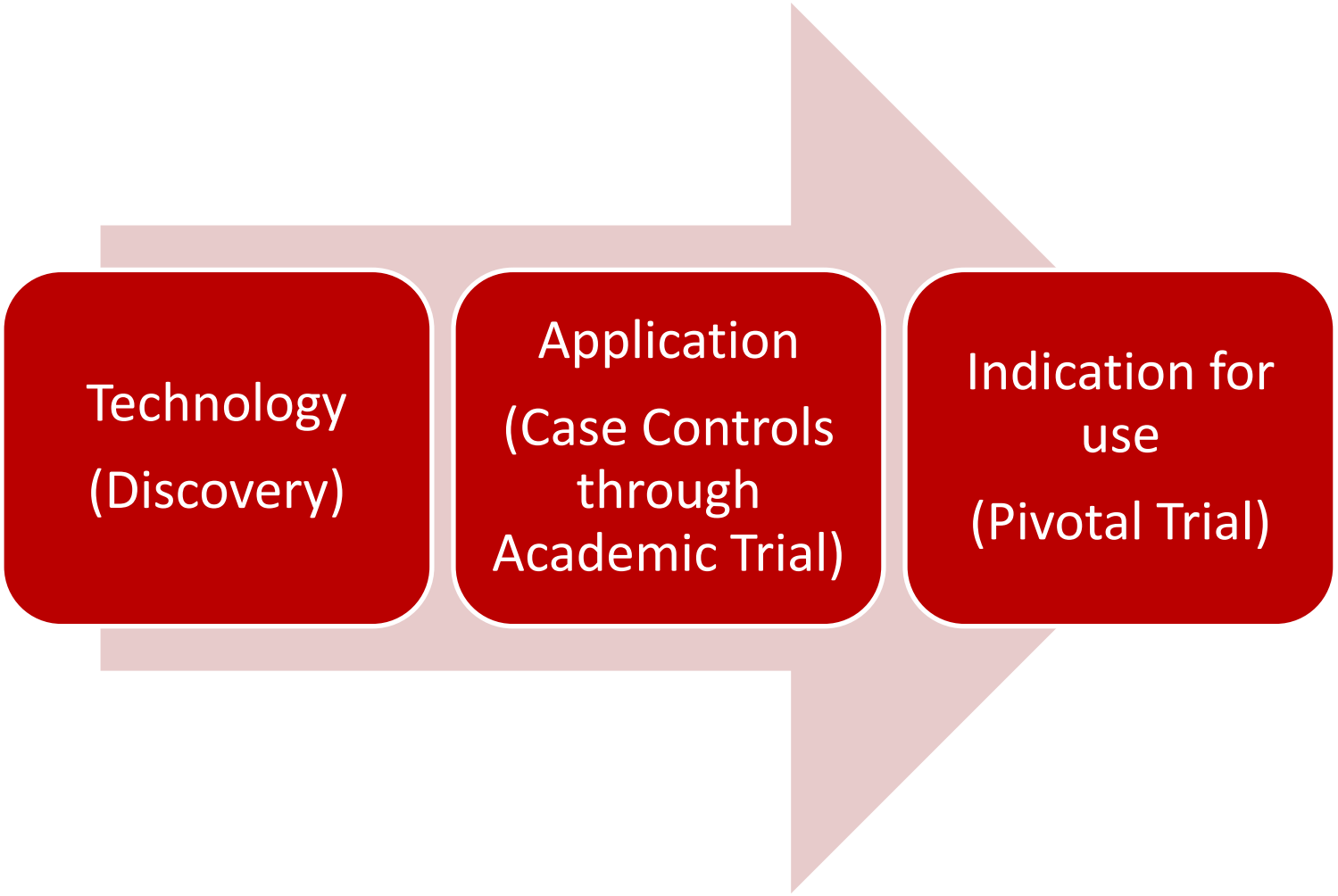
History of Septin 9…..the path to Clinical Utility



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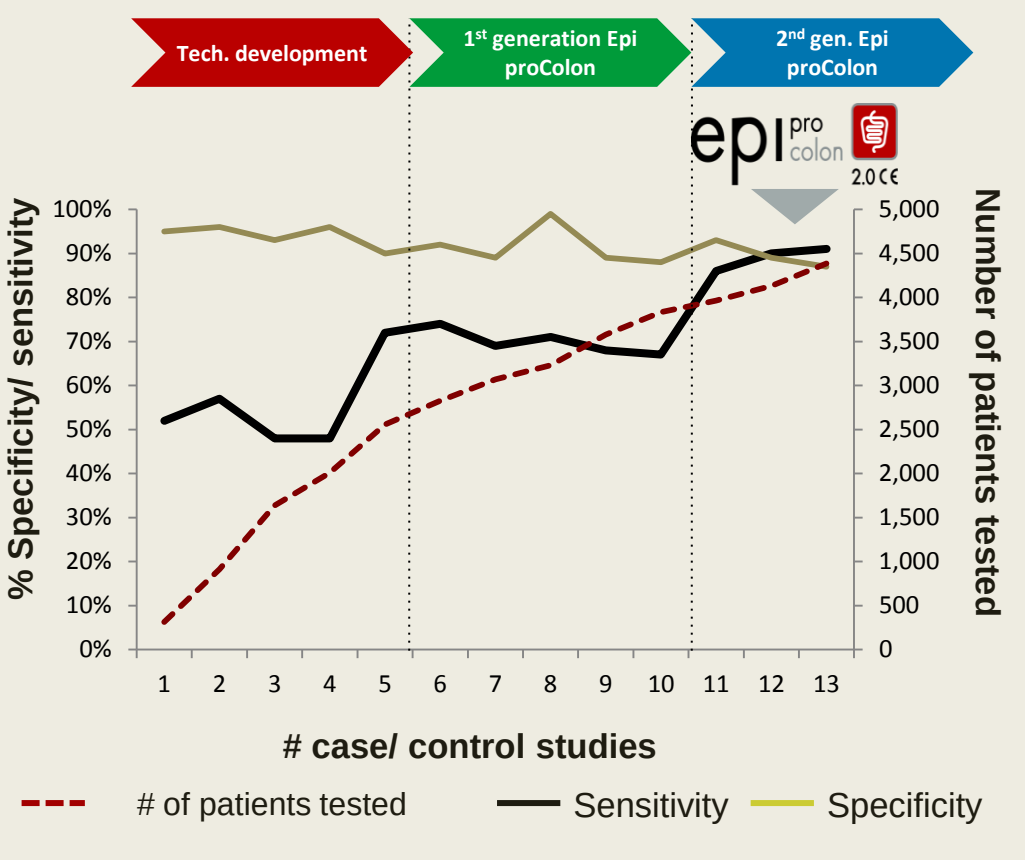
Epi proColon is extensively clinically validated yielding a strong performance and is endorsed by key opinion leaders

Overview of Epi proColon development



Key opinion leader support

Unfortunately, screening compliance remains low, partly due to patient dissatisfaction with faecal / endoscopic testing. A blood-based test providing clinically actionable CRC risk information would likely improve screening compliance and enhance clinical decision making."
Source: J. Cancer. 2010
Dr. Chong-Chin Liwe
Harvard Medical School/ Brigham and Women's Hospital

"It is clear that the convenience and simplicity of a plasma assay would be considerable."
Source: Clin. Cancer Res. 2006
Dr. Bernhard Lewin
University of Texas M.D. Anderson Cancer Centre

"The prospective PRESEPT study validates that a plasma-based marker can be used to detect preclinical colorectal cancer in asymptomatic individuals."
Prof. Thomas Rösch (Study Director PRESEPT/ Medical Director Dep. Interdisciplinary Endoscopy)
University Hospital Hamburg-Eppendorf

Epi proColon is the most extensively clinically validated blood test for early detection of colorectal cancer available on the market

Source: Company information

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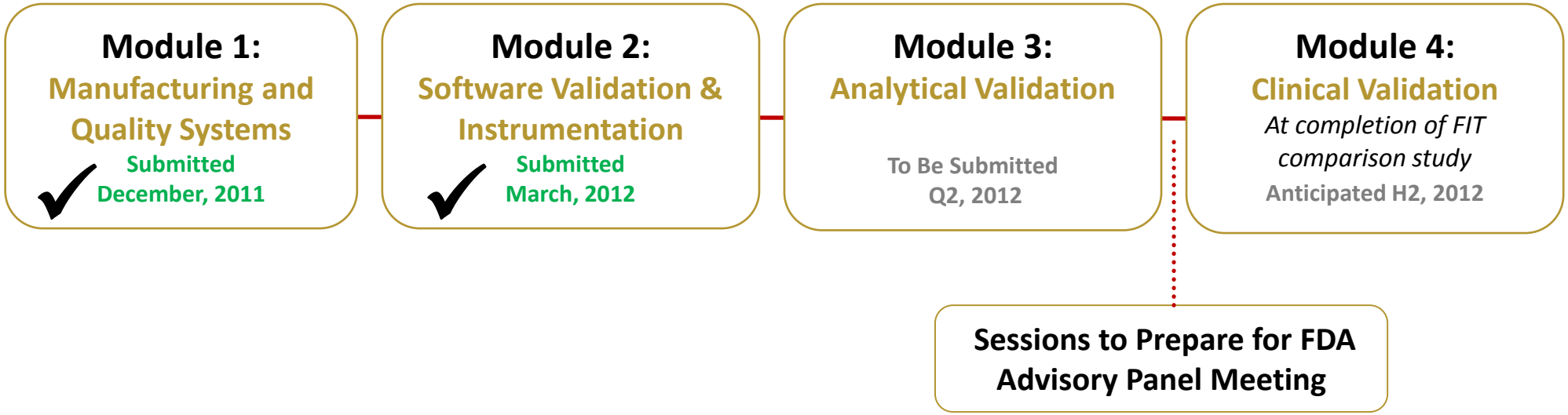
FDA Status: Modular Submission

FDA Premarket Approval Process



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Data Observations: Performance by Tumor Location

	PRESEPT	Pivotal	ARUP	Molnar Budapest
Proximal	76% n=21	64% n=14	80% n=10	94% n=36
Distal	60% n=30	70% n=30	91% n=37	96% n=56

Unlike colonoscopy and FIT, in multiple studies with Septin9, no significant difference was observed between proximal and distal tumors

Major DDW 2012 theme: variability in colonoscopy

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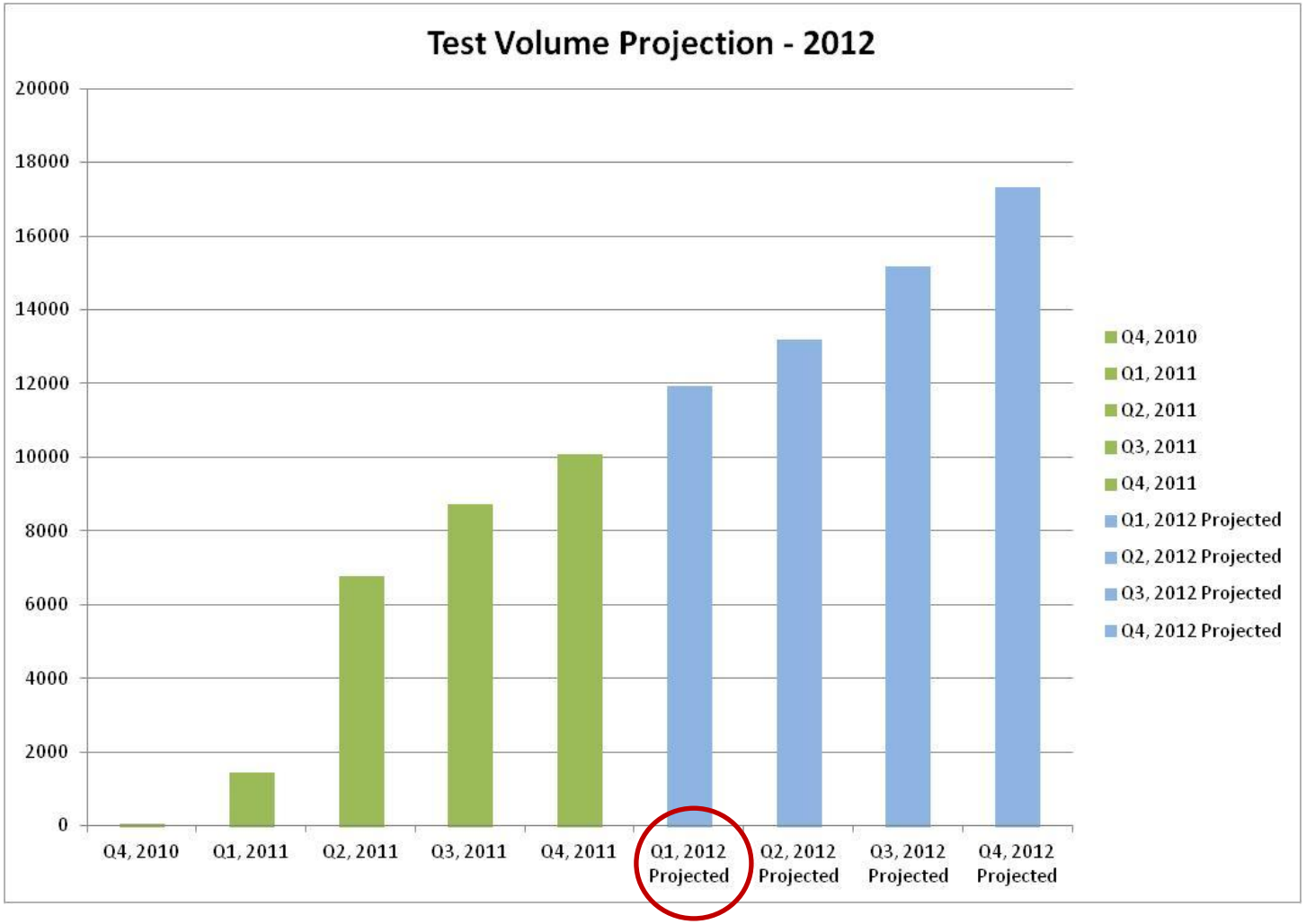
Septin9 Test Volume – LDT's (Colovantage, methylated Septin 9)



Estimate ~1000 tests per week being performed in the US, 5 cancers detected each week in blood

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CRC Current and Future Screening Modalities

	Colonoscopy	FOBT	FIT	Septin9	Cologuard™
Sample	N/A	Stool	Stool	Blood	Stool
Annual Volume	14 million	8 million	4 million	--	--
Cost ($ Reimbursement)	1000 - 4000	(4.61 NLR)	(22.53 NRL)	100 - 200 (est)	>300 (est)
Sensitivity: Cancer	95%	40%	66%	68%[1]	85%[2]
Sensitivity: Pre-cancer	76%	12%	22%	N/A	54%[2]
Specificity	90%	98%	95%	80%[1]	90%[2]
Availability	MDs	IVD	IVD	LDT (2013 IVD est)	(2013 IVD est)

Performance = sensitivity x utilization
"the best test is the one that gets done"

Source: USB Healthcare Services Conference New York NY 2/17/12 (Exact Sciences presentation with adaptations);
[1] Epigenomics press release 12/9/11; [2] Ahlquist DA et al. Gastroenterology 142:248-256 (2012)

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Issues (or what keeps me awake at night?)

- Imperfect Standards are firmly entrenched
  - Remember when culture was the gold standard rather than PCR in ID
  - Remember when self testing wasn't available?
  - How "perfect" is colonoscopy?
- Mis-aligned Incentives
  - Payment patterns are difficult to alter (provider,payer)
  - Rewards are disproportionally skewed to chemotherapy
- Innovation is Driven by the Small Players in a tough capital environment
  - Big Dx buys de-risked assays, Small dx cannot afford the up-front
- Clarity is absent
  - How would you describe the reward for a small dx company with a new cancer assay? How can you build a valid business model?
- CRO costs are out of line
  - Cancer

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Opportunities for Improvement

- Research partnerships: Driven by overlapping but different needs.
  - Pharma and DX are incredibly dissimilar…..customer , user, channel
  - Govt. research WW is not end user focused
- Too few care approaches allow full cost clarity (Kaiser? VA?)
- Inertia is driven by the imperfect standards and entrenched rewards structures
- Actively link the payment process via a visible mechanism to the Regulatory process (Japan?)
- Differentiate reward for differentiated regulatory credential of offering?

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The Path to Clinical Utilization of Septin 9

PMA

	2012	2013	2014	2015
Evidence development& Guideline Strategy	• PRECEPT Publication, • PIVOTAL publication • Variability of colonoscopy	• FIT Comparison publication • Other pubs	Further indications for the marker	
Coding & payment Strategy	Stacking	81401 utilization		Colonoscopy Changes
Payer Coverage strategy	• Mix analysis, • Targets • Payer Package	Senate /House engagement	Guideline Inclusion	
Positioning and pricing Strategy	• LDT Licenses	Complete Economic Model		

SEPTIN 9 DATA FOR CLINICAL UTILITY

TARGET VALIDATION	PROSPECTIVE DATA	FDA DATA	PLANNED TRIALS FOR CURRENT USE	FUTURE INDICATIONS
• 15 CASE CONTROL STUDIES • CE TRIAL	• 8000 PATIENT COHORT, ~ 1500 REPRESENTATIVE ASSAYS	• 8000 PATIENT COHORT,~1500 SELECTED ASSAYS • >2000 INTERNAL • FIT COMPARISON (300) • PRE/POST COLONOSCOPY • CIRCADIAN (100)	• ADHERENCE • FIT FOLLOW UP	• RECURRENCE • TUMOR BURDEN • HIGH RISK • FLEX SIG COMPANION
>4300 SAMPLES	> 1500 SAMPLES	~5000 SAMPLES	5000 EST.	

Difficult to combine FDA and reimbursement trials

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Demonstrating clinical Utility

- COLORECTAL CANCER RECOMMENDATIONS
  - Establish a registry of patients in trials that are apparent false positives
  - Identify a “platinum “standard to compensate for colonoscopy variability
- GENERAL CANCER RECOMMENDATIONS
  - Collect blood and tissue samples on all cancer patients to support
  - Create accelerated review and publication format for oncology/personalized medicine assays to overcome extended/biased review cycles in traditional publications
  - Link real world LDT performance experience to FDA filings

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When would a blood test have made a difference for Deanna?

- Missed tumor on initial mammogram(93)?
- Selection of chemo (95) post mastectomy"?
- 16 annual hi-res mammographies?
- Transfer to routine monitoring (06) ?
- 7 MDs call it pneumonia (june 2010)?
- 9/2010 when 10 tumors were found? What next?
- 8/13/54-9/29/10
- PERSONAL OPINION: perfect takes too long