# Lo studio Protèus: aggiornamenti

DANIELE REGGE

ISTITUTO PER LA RICERCA E LA CURA DEL CANCRO
CANDIOLO -TORINO

Prevenzione Serena, 9 Ottobre 2012

# Studio di accettabilità ed accuratezza diagnostica in un programma di screening del carcinoma colon-rettale. Confronto tra la colonoscopia virtuale con CAD e sigmoidoscopia. Verifica di un nuovo modello diagnostico basato sulla telediagnosi.

10 settembre 2008

# Studio Protèus

**Lo studio Protèus è un programma di prevenzione secondaria per l'identificazione dell'adenoma avanzato (lesione che ha una spiccata tendenza all'evoluzione verso il carcinoma invasivo)**

## Obiettivo principale

Confrontare il tasso d'adesione e il tasso d'identificazione delle lesioni del CCR di CTC e RSS in un programma di prevenzione

## Dimensione campionaria

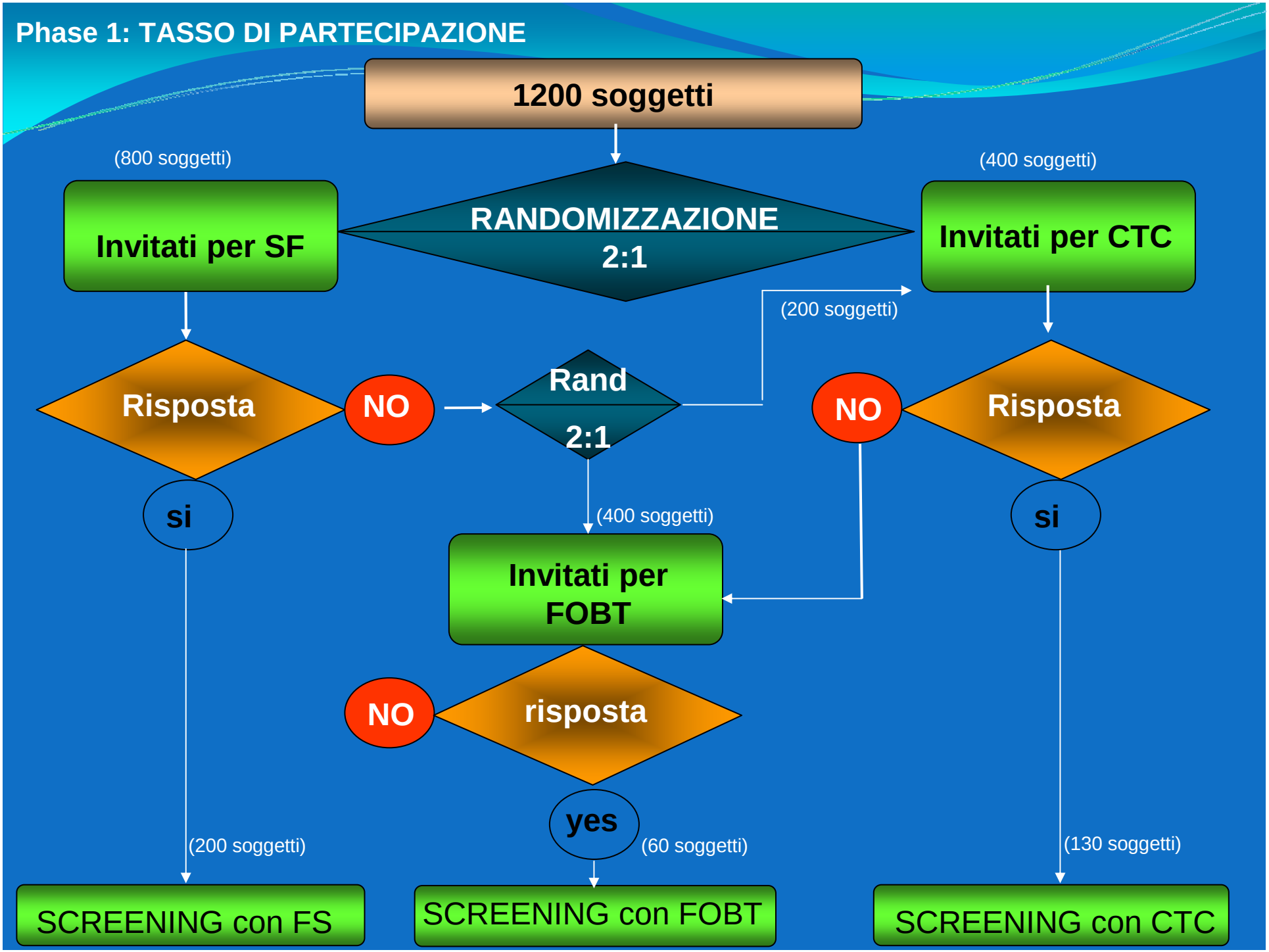
Circa 25.000 soggetti. Lo studio è stato dimensionato per identificare un aumento della tasso d'identificazione della CTC verso la RSS di almeno il 10% e del tasso d'adesione di almeno il 2%.

## Disegno

Multicentrico, prospettico, a due braccia (FS vs CTC). Per evitare bias di selezione lo studio è disegnato in due fasi. Nella fase 1 è aggiunto un braccio CTC verso FOBT nei non aderenti. La valutazione della CTC è eseguita con l'aiuto del CAD e in telediagnosi.

## Criteri d'inclusione

Asintomatici, rischio intermedio, 58 anni


Phase 1: TASSO DI PARTECIPAZIONE
1200 soggetti
(800 soggetti)
Invitati per SF
RANDOMIZZAZIONE
2:1
(400 soggetti)
Invitati per CTC
(200 soggetti)
Risposta
NO
Rand
2:1
NO
Risposta
si
(400 soggetti)
si
Invitati per
FOBT
NO
risposta
yes
(60 soggetti)
(200 soggetti)
(130 soggetti)
SCREENING con FS
SCREENING con FOBT
SCREENING con CTC

# Phase 2: TASSO DI IDENTIFICAZIONE

# Centri Partecipanti

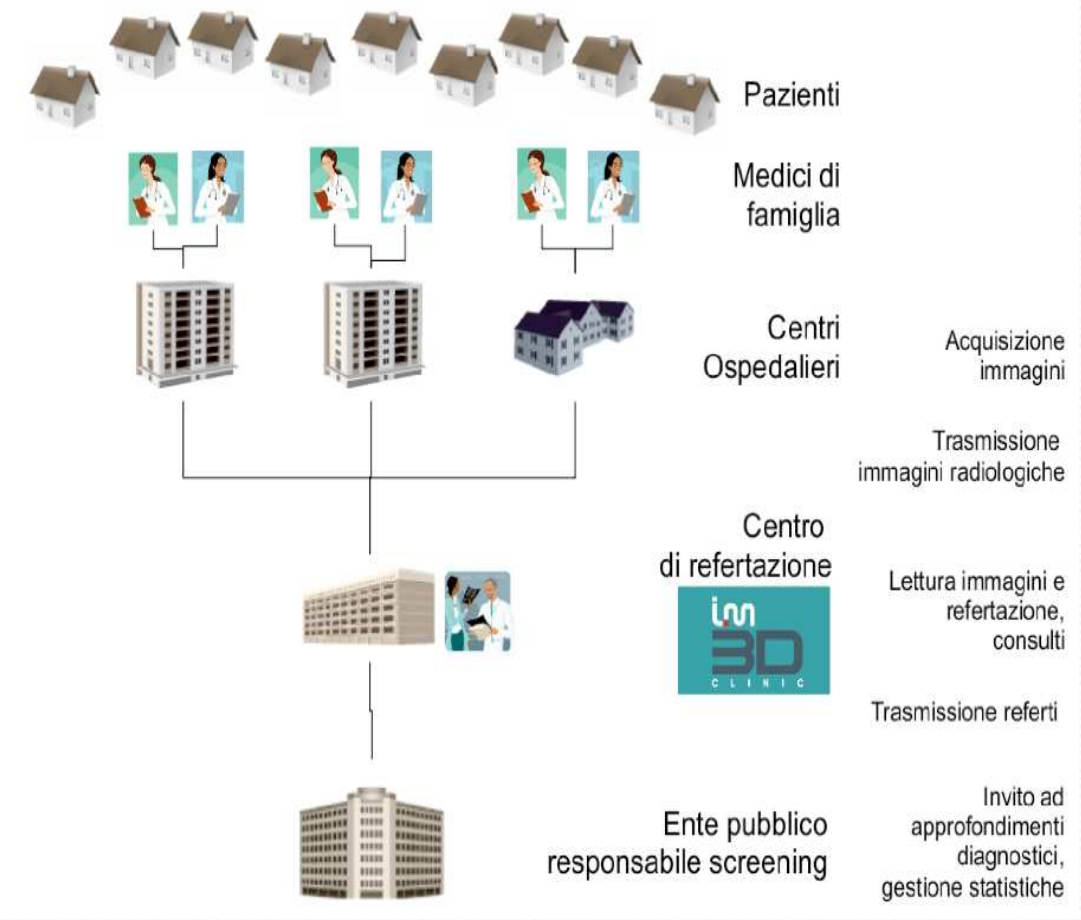
- Torino
  - Molinette
  - San Giovanni Bosco
  - IRCC
- Biella
- Novara
- Veruno-Borgomanero
- Azienda Ospedaliera Verona


VERBANIA
Veruno-Borgomanero
Biella
BIELLA
NOVARA
Novara
VERCELLI
TORINO
ASTI
ALESSANDRIA
Ospedale Molinette
Ospedale SGAS
Ospedale San Giovanni Bosco
IRCC - Candiolo
CUNEO


Belluno
Treviso
Vicenza
Venezia
Verona
Padova
Rovigo
Az. Ospedaliera Verona

# Acquisizione distribuita e lettura centralizzata

- **Acquisizione** degli esami **distribuita** sul territorio per avvicinarsi al soggetto target e favorire così un aumento di adesione
- **Centralizzazione** della **lettura** per favorire la standardizzazione del servizio e la costituzione di un archivio completo e un pool di lettori esperti
- Uso delle tecnologie **CAD** per ridurre i costi assicurando la necessaria accuratezza diagnostica



# Esperienza

- Non è stabilita una soglia di numero di esami refertati al di sopra della quale un radiologo è considerato esperto
- ACRIN: > 500 esami refertati + corso + esame finale
- IMPACT: > 50 esami refertati
- Il successo della sperimentazione è determinata da:
  - Qualità tecnica (corsi per TSRM e IP)
  - Qualità di refertazione (corso per radiologi con test finale)

# Participation and yield of colonoscopy versus non-cathartic CT colonography in population-based screening for colorectal cancer: a randomised controlled trial

Esther M Stoop*, Margriet C de Haan*, Thomas R de Wijkerslooth, Patrick M Bossuyt, Marjolein van Ballegooijen, C Yung Nio, Marc J van de Vijver, Katharina Biermann, Maarten Thomeer, Monique E van Leerdam, Paul Fockens, Jaap Stoker, Ernst J Kuipers, Evelien Dekker

## Summary

**Background** Screening for colorectal cancer is widely recommended, but the preferred strategy remains unidentified. We aimed to compare participation and diagnostic yield between screening with colonoscopy and with non-cathartic CT colonography.

**Methods** Members of the general population, aged 50–75 years, and living in the regions of Amsterdam or Rotterdam, identified via the registries of the regional municipal administration, were randomly allocated (2:1) to be invited for primary screening for colorectal cancer by colonoscopy or by CT colonography. Randomisation was done per household with a minimisation algorithm based on age, sex, and socioeconomic status. Invitations were sent between June 8, 2009, and Aug 16, 2010. Participants assigned to CT colonography who were found to have one or more large lesions (≥10 mm) were offered colonoscopy; those with 6–9 mm lesions were offered surveillance CT colonography. The primary outcome was the participation rate, defined as number of invitees undergoing the examination relative to the total number of invitees. Diagnostic yield was calculated as number of participants with advanced neoplasia relative to the total number of invitees. Invitees and screening centre employees were not masked to allocation. This trial is registered in the Dutch trial register, number NTR1829.

**Findings** 1276 (22%) of 5924 colonoscopy invitees participated, compared with 982 (34%) of 2920 CT colonography invitees (relative risk [RR] 1·56, 95% CI 1·46–1·68; p<0·0001). Of the participants in the colonoscopy group, 111 (9%) had advanced neoplasia of whom seven (<1%) had a carcinoma. Of CT colonography participants, 84 (9%) were offered colonoscopy, of whom 60 (6%) had advanced neoplasia of whom five (<1%) had a carcinoma; 82 (8%) were offered surveillance. The diagnostic yield for all advanced neoplasia was 8·7 per 100 participants for colonoscopy versus 6·1 per 100 for CT colonography (RR 1·46, 95% CI 1·06–2·03; p=0·02) and 1·9 per 100 invitees for colonoscopy and 2·1 per 100 invitees for CT colonography (RR 0·91, 0·66–2·03; p=0·56). The diagnostic yield for advanced neoplasia of 10 mm or more was 1·5 per 100 invitees for colonoscopy and 2·0 per 100 invitees for CT colonography, respectively (RR 0·74, 95% CI 0·53–1·03; p=0·07). Serious adverse events related to the screening procedure were post-polypectomy bleedings: two in the colonoscopy group and three in the CT colonography group.

**Interpretation** Participation in colorectal cancer screening with CT colonography was significantly better than with colonoscopy, but colonoscopy identified significantly more advanced neoplasia per 100 participants than did CT colonography. The diagnostic yield for advanced neoplasia per 100 invitees was similar for both strategies, indicating that both techniques can be used for population-based screening for colorectal cancer. Other factors such as cost-effectiveness and perceived burden should be taken into account when deciding which technique is preferable.

**Funding** Netherlands Organisation for Health Research and Development, Centre for Translational Molecular Medicine, and the Nuts Ohra Foundation.

## IL TEST DI VALUTAZIONE

- Il test di valutazione che si svolgerà il terzo giorno avrà l'obiettivo di selezionare i lettori coinvolti nel progetto di screening sperimentale della Regione Piemonte *(progetto Protéus)*.

## BOARD SCIENTIFICO

- Dott. **Daniele Regge** *(UOA Radiodiagnostica, IRCC Candiolo)*,
- Dott. **Carlo Senore** *(CPO Piemonte)*,
- Dott.ssa **Loredana Correale** *(im3D)*

## RELATORI

- **Delia CAMPANELLA**, *Candiolo*
- **Loredana CORREALE**, *Torino*
- **Paolo FALCO**, *Torino*
- **Franco IAFRATE**, *Roma*
- **Gabriella IUSSICH**, *Candiolo*
- **Andrea LAGHI**, *Latina*
- **Emanuele NERI**, *Pisa*
- **Daniele REGGE**, *Candiolo*
- **Carlo SENORE**, *Torino*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CON IL CONTRIBUTO DI:

REGIONE PIEMONTE

im3D

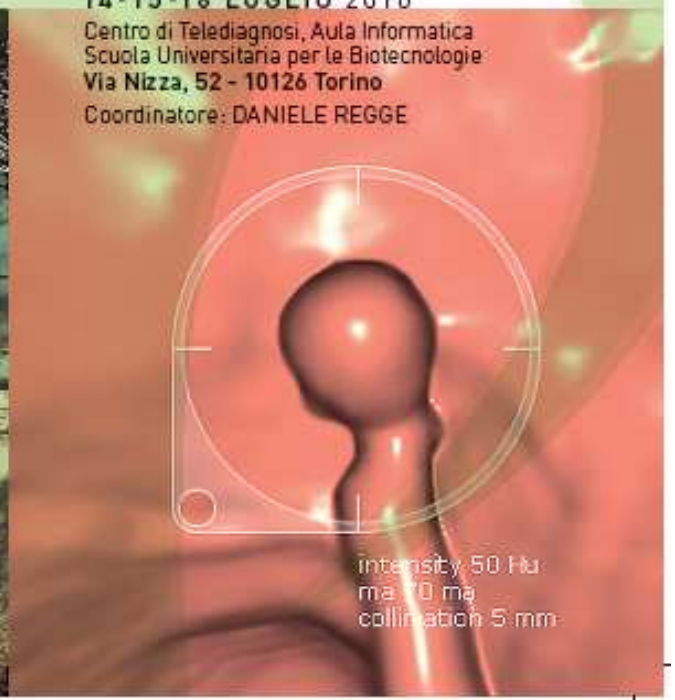
PROTEUS
PREVENZIONE COLON

# COLONSCOPIA VIRTUALE E PREVENZIONE

## CORSO AVANZATO DI SCREENING

**14·15·16 LUGLIO** 2010

Centro di Telediagnosi, Aula Informatica
Scuola Universitaria per le Biotecnologie
**Via Nizza, 52 - 10126 Torino**
Coordinatore: DANIELE REGGE



# Obiettivi secondari

- Accettabilità e sicurezza dei test di screening
- Eventi avversi
- Impatto del modello organizzativo di telediagnosi sui costi

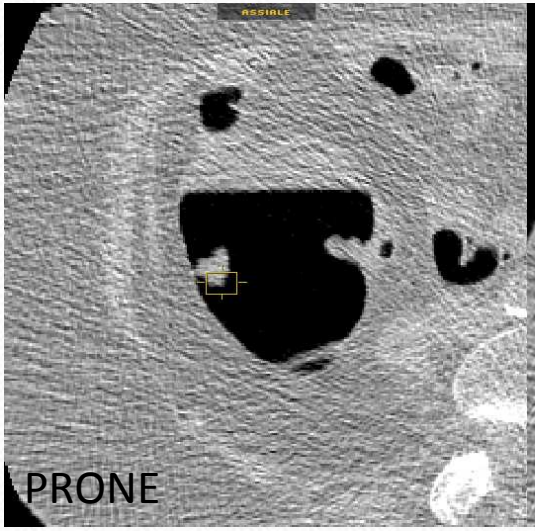
# Studi preliminari

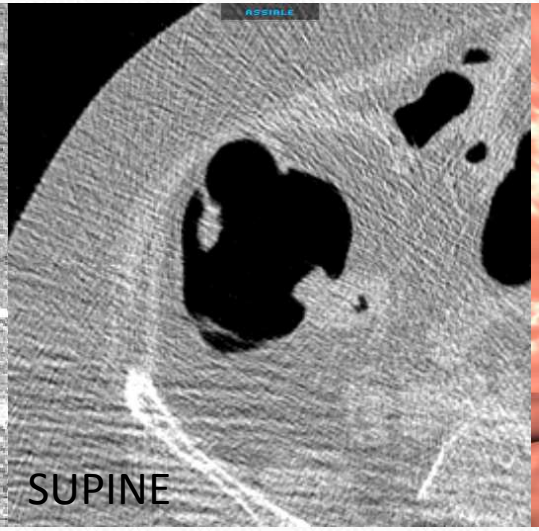
- Valutazione dell’accuratezza del CAD in soggetti che eseguono l’esame con marcatura fecale (doppia lettura/CAD primo lettore verso lettura non assistita)

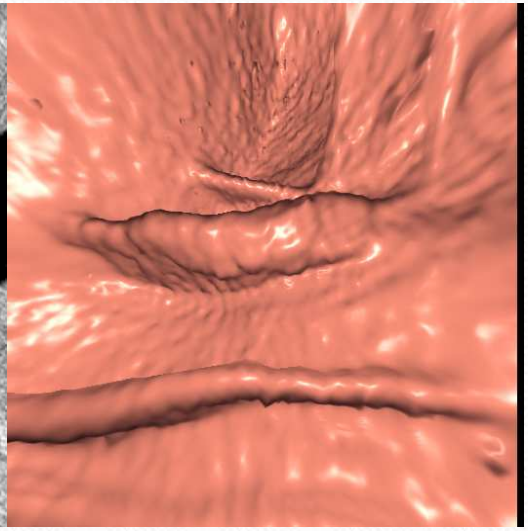
- Qualità dell’esame e tolleranza alla preparazione con marcatura fecale

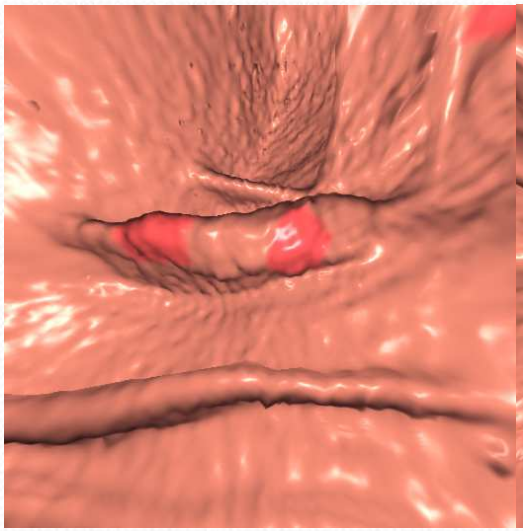
- Confronto dell’accuratezza diagnostica e tempi di lettura con differenti modalità CAD

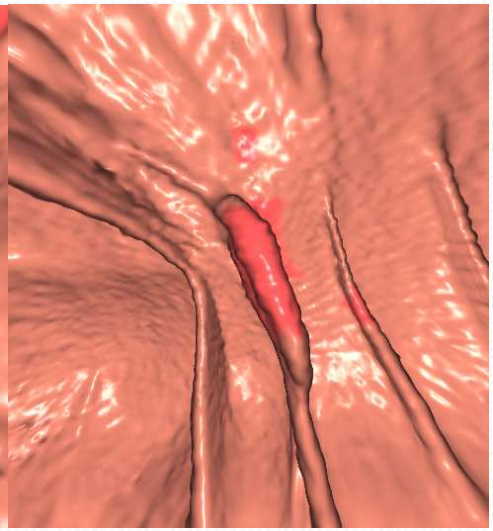
# CAD can help pin-point lesion



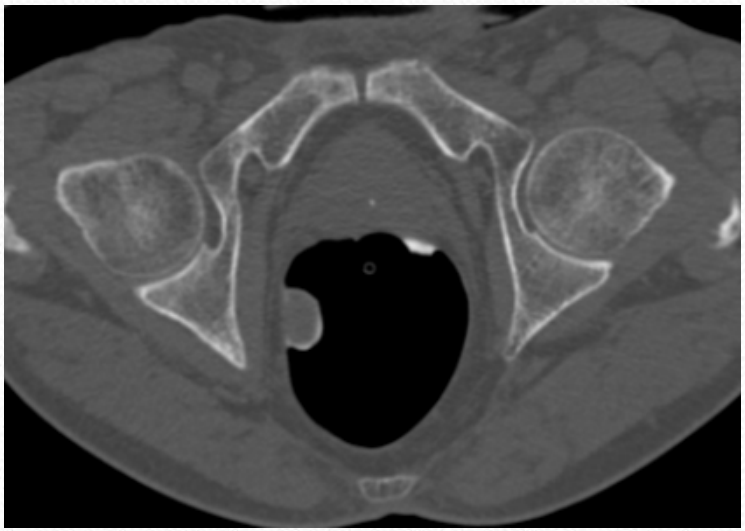




17 mm flat lesion of the ascending colon not seen by the radiologist

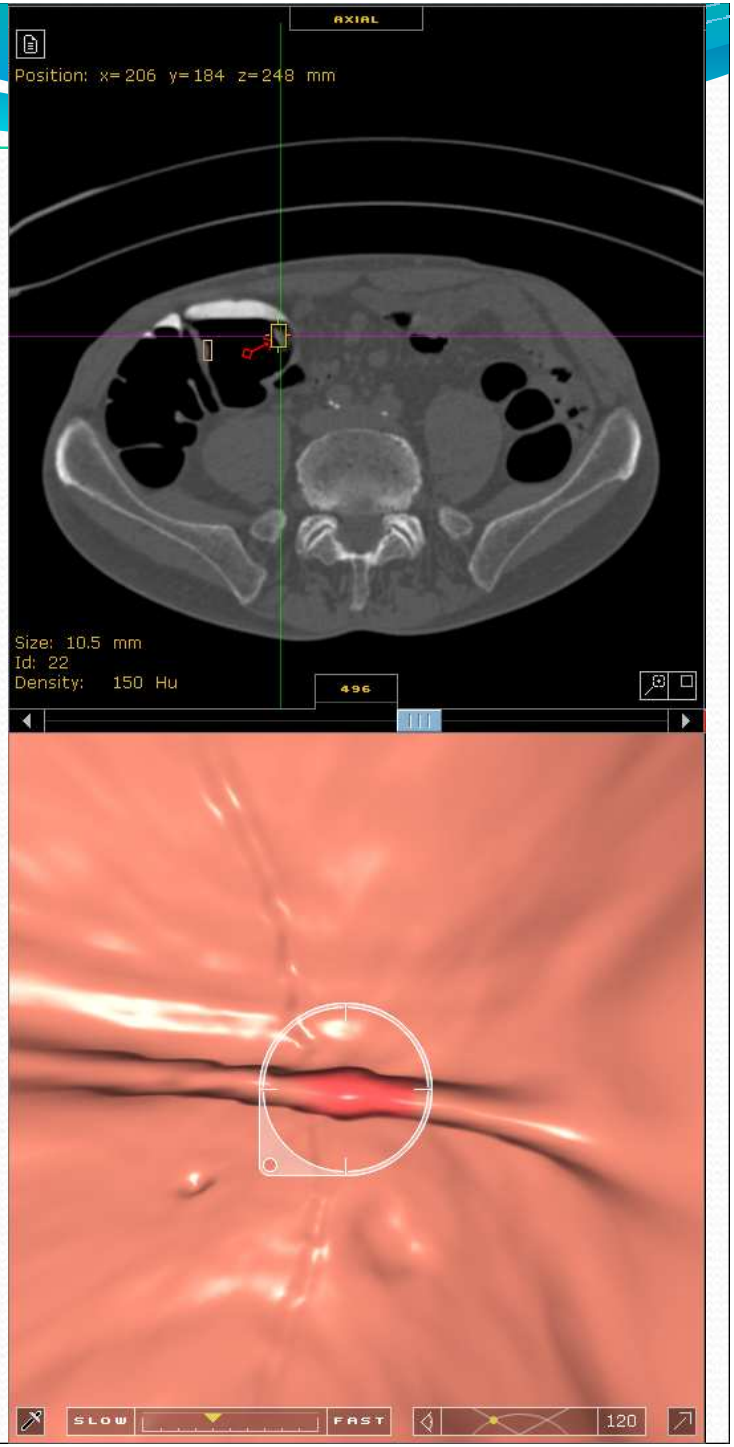
tubular polyp, severe grade dysplasia

# 2° READER



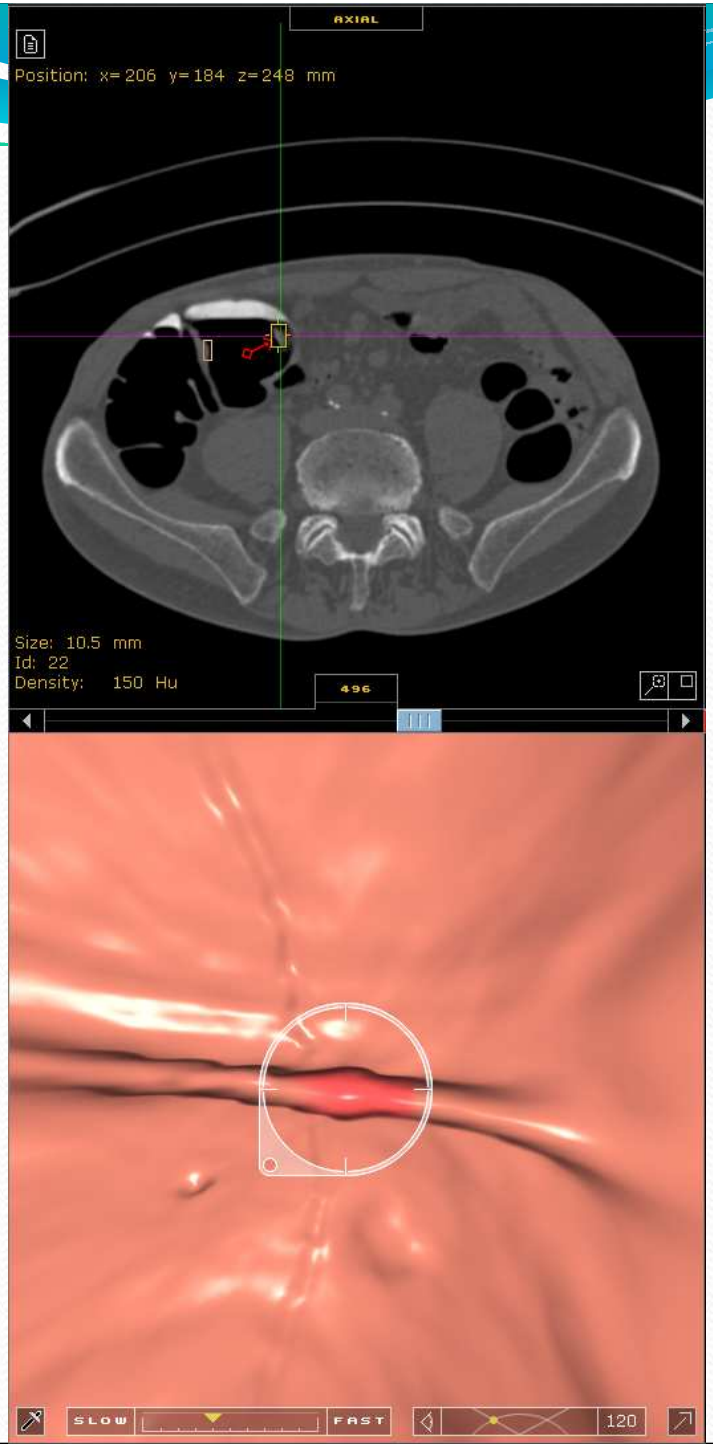
5 -15 min

| TYPE | DISTANCE | DIAMETER |
|---|---|---|
| P | 5.4 | 23.0 |
| C | 27.6 | 7.9 |
| C | 45.7 | 3.0 |
| C | 102 | 5.0 |
| C | 130 | 8.6 |
| C | 155 | 8.0 |
| C | 155 | 3.3 |
| C | 160 | 10.5 |
| C | 161 | 9.9 |
| C | 162 | 11.2 |



# 1° READER

| TYPE | DISTANCE | DIAMETER |
|---|---|---|
| P | 5.4 | 23.0 |
| C | 27.6 | 7.9 |
| C | 45.7 | 3.0 |
| C | 102 | 5.0 |
| C | 130 | 8.6 |
| C | 155 | 8.0 |
| C | 155 | 3.3 |
| C | 160 | 10.5 |
| C | 161 | 9.9 |
| C | 162 | 11.2 |



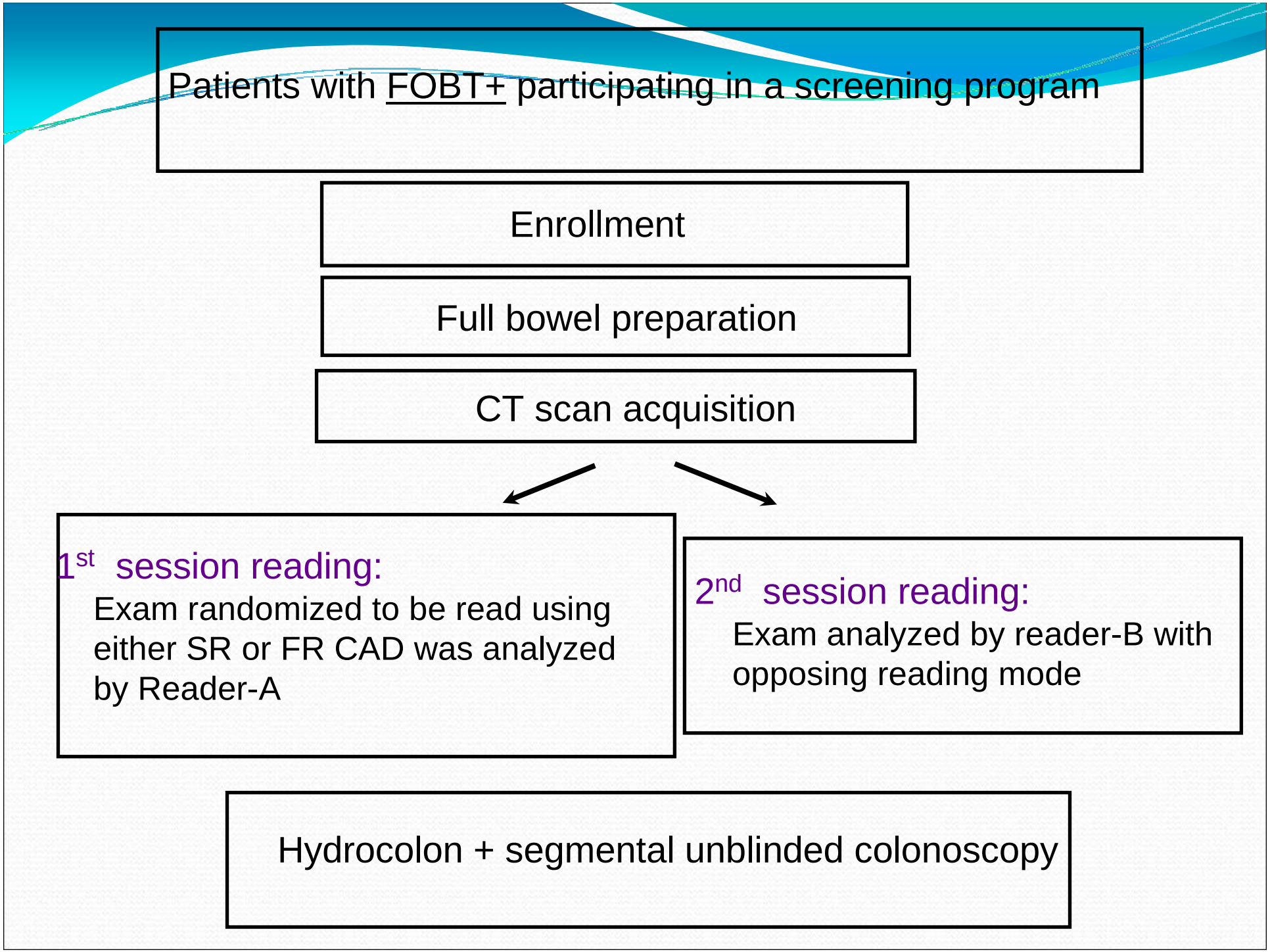

2-4 min

# Studio preliminare 1

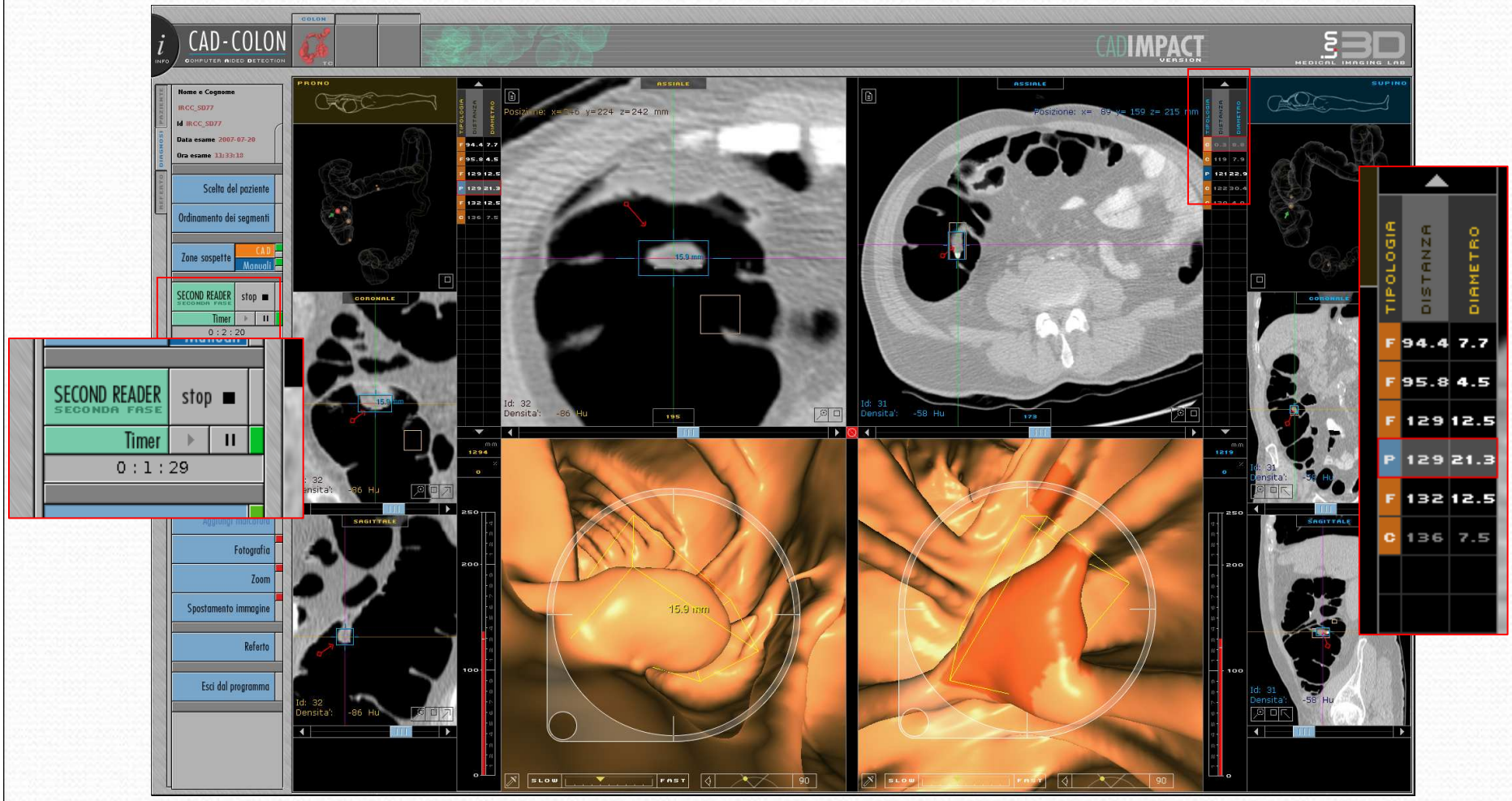
**Reporting Computed Tomographic Colonography (CTC): preliminary assessment of a new double-read paradigm that uses Computer-aided Detection (CAD) as the first-reader.**

**Purpose:** To compare sensitivity, specificity and time-efficiency of unassisted interpretation with that of a double reading paradigm where computer-aided detection is the first reader (DR CAD-FR).
**Materials and Methods:** After Ethical Committee approval, three experienced radiologists interpreted 155 CTC studies, of whom 57 contained 10 masses and 79 polyps ≥ 6-mm. Reading was randomized to either unassisted or DR CAD-FR; studies were reared 6 weeks later using the opposite reading paradigm. DR CAD-FR consists in the evaluation of a list of CAD generated marks followed by a fast 2D unassisted review for mass detection. Per-patient sensitivity, specificity, reporting times were compared using paired exact and Student's *t* test. For each mode, association between missed polyps and lesions characteristics were explored by multiple regression analysis.
**Results:** With an average number of 10 (SD=7) false-positives per scan, stand-alone CAD sensitivity was 91%. Sensitivity and specificity was 74% (95% CI 66-81) and 94% (95%CI 82-95) for unassisted read respectively, 77% (95% CI 70,83) and 90% (95% CI 87-94) for DR CAD-FR respectively (P=0.6 and P=0.2). Overall unassisted and DR CAD-FR reporting times did not differ (243 versus 239 seconds; (P=0.6); however DR CAD-FR was faster when the number of CAD-marks per scan was 10 or less (187 versus 220 seconds, P=0.0004). Both modalities most likely missed small polyps, flat lesions and polyps visible in only one scan.

**Conclusion:** DR CAD-FR paradigm had similar performance as compared to unassisted interpretation but better time-efficiency when an adequate number of CAD prompts was generated. Inconspicuous polyps were equally difficult to detect with the 2 reading modes.

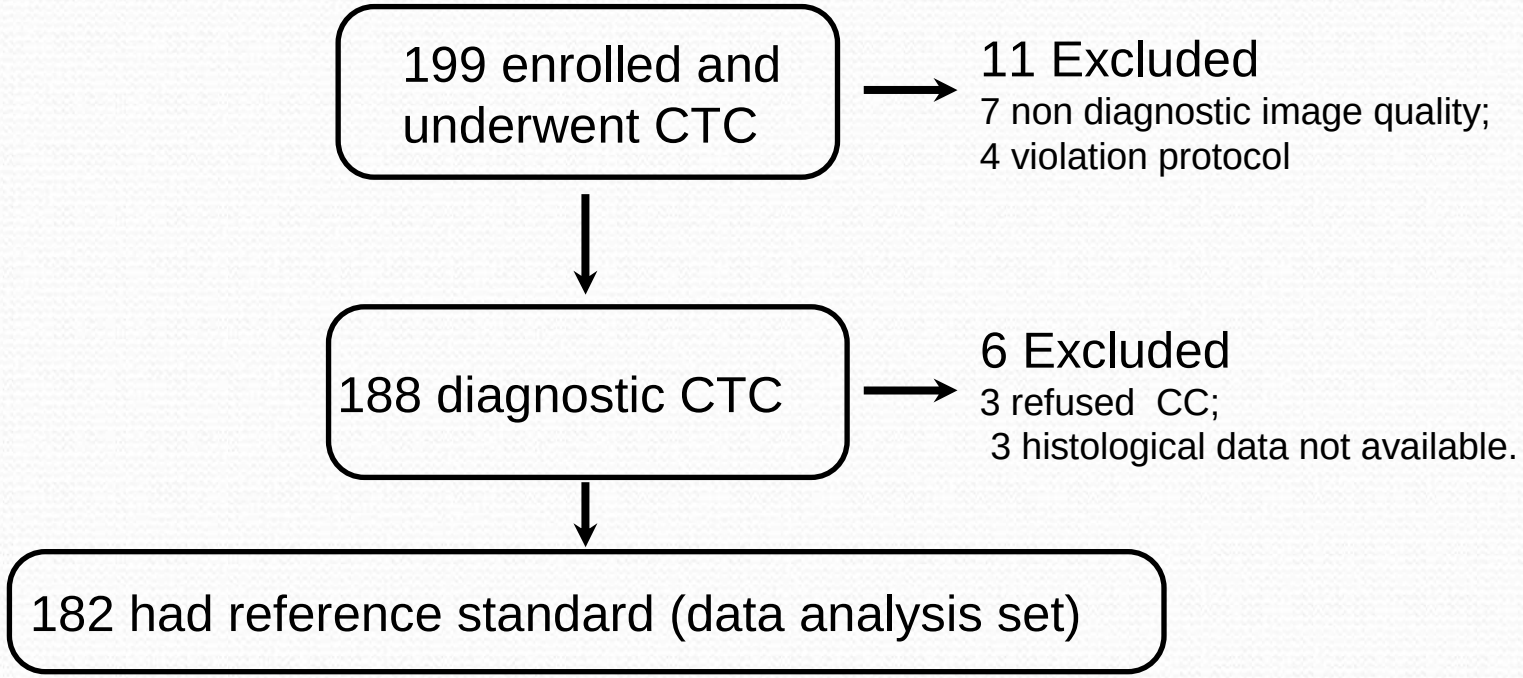

Patients with FOBT+ participating in a screening program
Enrollment
Full bowel preparation
CT scan acquisition
1st session reading:
Exam randomized to be read using either SR or FR CAD was analyzed by Reader-A
2nd session reading:
Exam analyzed by reader-B with opposing reading mode
Hydrocolon + segmental unblinded colonoscopy

# Software was customized specifically for CAD-IMPACT trial




CT scan is promptly archived in anonymous form

# Patient population




89 Negative

- 58 No Lesion
- 6 Advanced adenoma ≤ 5 mm
- 17 Low risk adenoma ≤ 5
- 8 Non-adenomatous lesions

93 Positive (cancer or adenoma ≥ 6 mm)

- 13 Cancer ≥ 10 mm
- 48 Advanced adenoma ≥ 10 mm
- 15 Advanced adenoma 6-9 mm
- 17 Low risk adenoma 6-9 mm

# Results: per patient analysis (≥6mm)

## Double Reading Paradigms

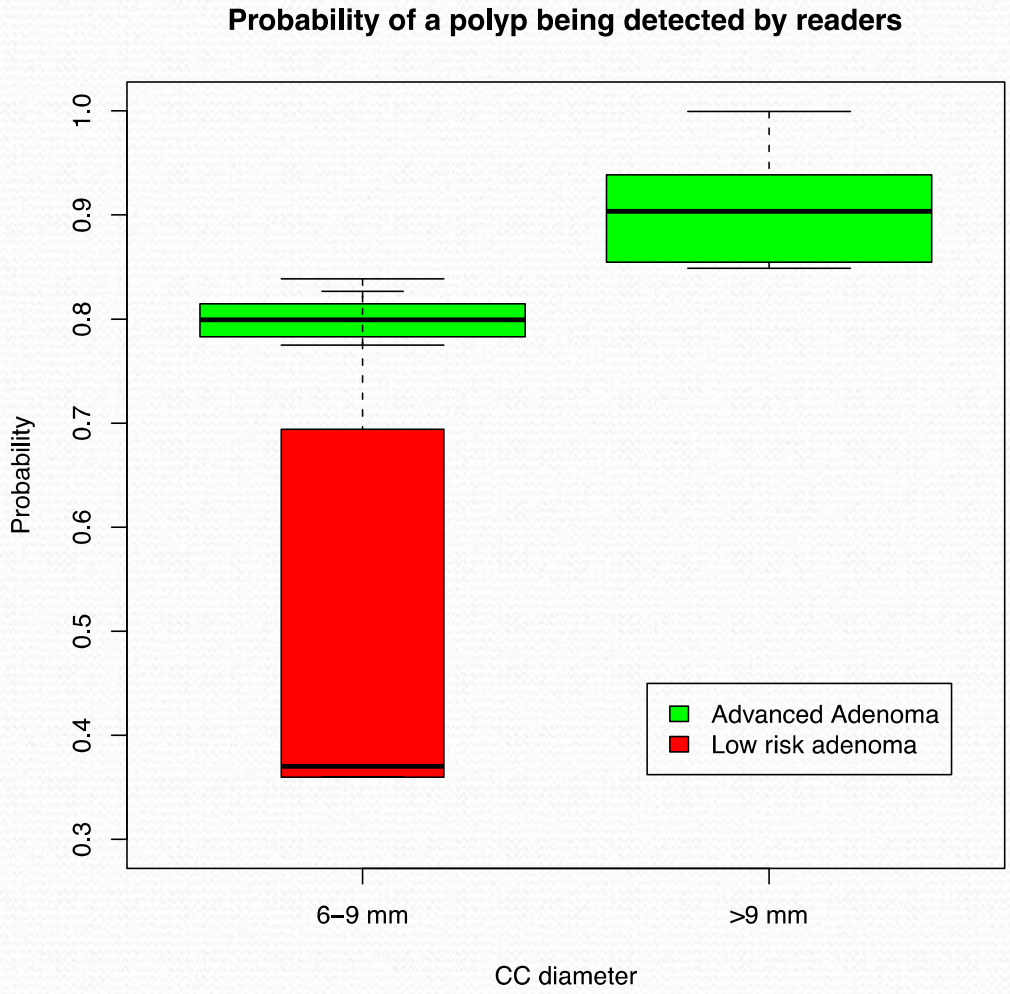
| | CAD Second Reader | | CAD First Reader | |
|---|---|---|---|---|
| | Unassisted reading | Radiologist + CAD | CAD | CAD + Radiologist |
| Sensitivity (%) | 80 (74/93) (70,87) | 86 (80/93) (77,92) | 85 (79/93) (75,91) | 89 (83/93) (81,95) |
| Specificity (%) | 92 (82/93) (82,97) | 90 (80/89) (82,95) | 93 (83/93) (86,97) | 91 (81/93) (83,96) |
| PPV (%) | 91 (74/81) (83,96) | 90 (80/89) (82,95) | 92 (78/84) (85,97) | 91 (83/91) (83,96) |
| AUC | 0.86 ± 0.04 | 0.90 ± 0.03 | 0.92 ± 0.02 | 0.94 ± 0.02 |

The difference in sensitivity between SR and DR with FR CAD was not statistically significant (P=0.5)

Compared to the Unassisted reading, CAD increased sensitivity for both reading paradigm (P=0.03)

For both CAD reading modes, the AUcs increased with CAD (P=0.02)

# Results: predicted probabilities from logistic model




- The likelihood of a polyp being correctly detected by readers increases with CC diameter (P=0.03).
- Small advanced adenoma were more likely confirmed after CAD prompting than LR adenoma (P=0.01).

# Reading Time

| Reading Paradigm | Interpretation Time | | |
|---|---|---|---|
| | **Phase 1** | **Phase II** | **TOT** |
| Double reading CAD Second Reader | 318 ± 27 sec | 177 ± 20 sec | 495 ± 38 sec |
| Double reading CAD First Reader | 276 ± 20 sec | 108 ± 8 sec | 384 ± 22 sec |

Double reading CAD FR reporting time was significantly shorter than double reader CAD SR (p=0.001)

# Studio principale: soggetti randomizzati (ott 2012)

| Soggetti randomizzati per gruppo 2011-2012 | | | | | |
|---|---|---|---|---|---|
| | **Torino** | **Biella** | **Novara** | **Verona** | **Totale** |
| **FS** | 6688 | 1610 | 601 | 1825 | 10724 |
| **CTC** | 5977 | 1472 | 601 | 888 | 8938 |
| | 12665 | 3082 | 1202 | 2713 | 19662 |

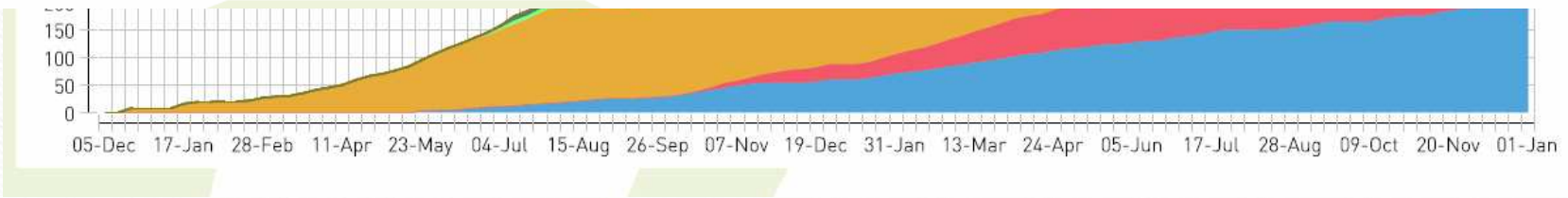
# Adesione allo studio 2012

| | Torino | | Biella | | Novara | | Verona | |
|---|---|---|---|---|---|---|---|---|
| **Invitati** | **3953** | | **1541** | | **516** | | **1404** | |
| **Rifiuto** | 12 | 0,3% | 13 | 0,8% | 0 | 0,0% | 0 | 0,0% |
| **App in sospeso** | 106 | 2,7% | 14 | 0,9% | 27 | 5,2% | 44 | 3,1% |
| **Aderenti** | 542 | 13,7% | 199 | 12,9% | 75 | 14,5% | 206 | 14,7% |
| **Totale risposte** | 660 | **16,7%** | 226 | **14,7%** | 102 | **19,8%** | 250 | **17,8%** |

# Studio principale

**Rapporto pazienti reclutati per centro**

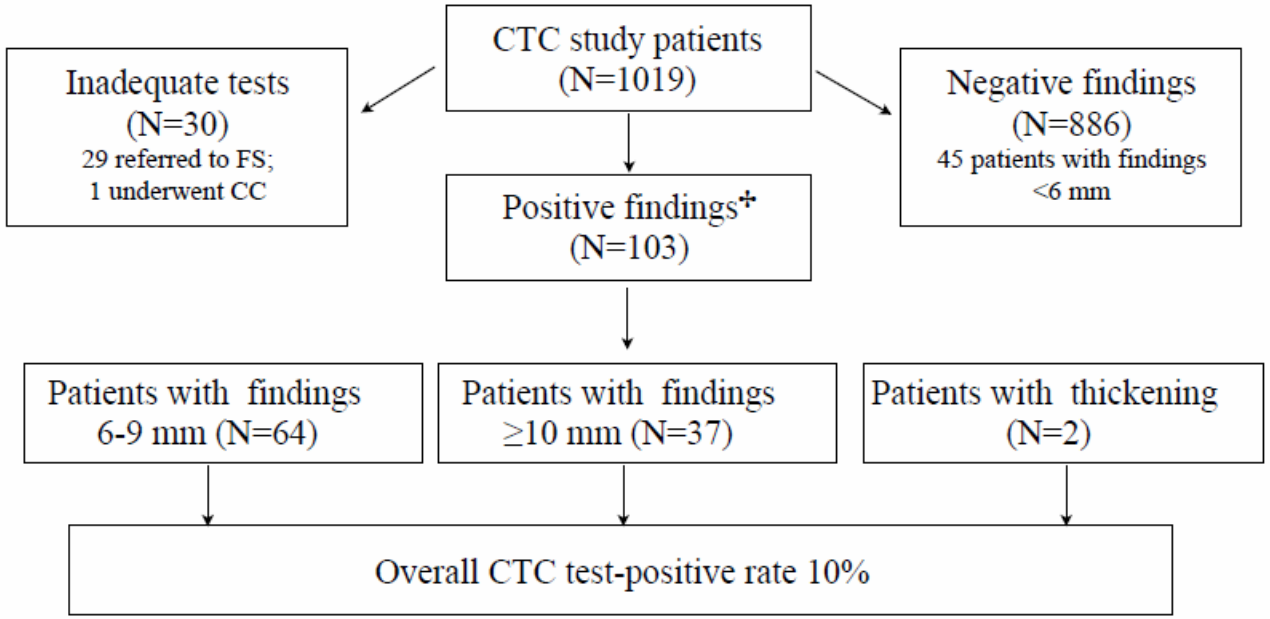

| | | Biella | Ospedale Mauriziano | Radiologia IRCC CANDIOLO | Radiologia Molinette 4 | Radiologia Molinette 7 | Verona Borgo Trento | Verona S.Bonifacio | Veruno | **TOTALE** |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Pazienti | Pazienti | Pazienti | Pazienti | Pazienti | Pazienti | Pazienti | Pazienti | **Pazienti** |
| | novembre | | | | | | | | 1 | 1 |
| | | 5 | 4 | | 5 | 5 | 3 | 9 | 4 | 35 |
| | | 5 | 3 | | 5 | 5 | 1 | 5 | 1 | 25 |
| | | 5 | | | 5 | 5 | | 2 | 1 | 18 |
| | | 5 | | | 4 | 5 | | | | 14 |
| | dicembre | | | | | 5 | | | | 5 |
| | | | | | | 3 | | | | 3 |
| Grand Total | | 195 | 136 | 310 | 205 | 212 | 88 | 134 | 75 | **1355** |



# Controllo di qualità

- *Qualità degli esami*
  - Buona/ottima 74%
  - Moderata 22,7%
  - Scadente 3% (32/1019)
- *Tagging insufficiente* 7,5% (77/1019)
- *Distensione insufficiente* 2,9% (30/1019)

# Tasso d'invio alla colonscopia 10%




**+ Positive for colonic masses/ polyps ≥6 mm**

Il CAD ha identificato il 92% delle lesioni

# COCOS trial (Netherlands)

- Results of the COCOS trial (Rand CTC versus colonoscopy, > 982-1276 cases).
- Referral to colonoscopy 9% (<9mm). Other 8% f/u (6-9mm polyps). Total 17%
- Participation rate: 34% CTC versus 22% colonoscopy


COCOS: VC vs Colonoscopy
SIGGAR: VC vs Colonoscopy, VC vs BE (symptomatic)
PROTEUS: VC vs Colonoscopy
SAFE: VC vs FOBT
Traffico
Altro...
Mappa
Satellite
©2010 Google - Map data ©2010 Basarsoft, PPWK, TeleAtlas, Transnavicom