BICKGROUND 2 AIMS: We followed up 494,187 participants from the first round of a regional biomal FIT screening from 32140 (cuceff value for positivity, 20 g hemgelobing faces) for multivariate Poisson regression models. RENUTS: Execute the second and the first round, a significant 20% to 30% decrease was found in the proportion of mean with a positive FIT result (From 5.7 to 1.4 per 1000), and the fifth round in which a positive FIT result (From 5.7 to 1.4 per 1000), and the fifth round in the first round in multivariate Poisson regression models. RESULTS: Execute the second and the first round in multivariate provide results from solution of a regional biology to result and advanced adv	Results of Compliant Participation in Five Rounds of Fecal Immunochemical Test Screening for Colorectal Cancer Flavia Baldacchini, 'Lauro Bucchi,' Orietta Giuliani, 'Silvia Mancini,' Alessandra Ravaioli, 'Rosa Vattiato,' Paolo Giorgi Rossi, [‡] Cinzia Campari, [®] Debora Canuti, 'Enza Di Felice,'' Francesca Mezzetti, 'Priscilla Sassoli de Blanchi, ¹ Stefano Ferretti, ⁴ and Fabio Falcini,**' on behalf of the Emilia-Romagna Region Workgroup for Colorectal Screening Evaluation ************************************		Clinical Gastroenterology and Hepatology 2020;∎:∎-■
Security of Compliant Participation in Five Rounds of Fecal Innunochemical Test Screening for Colorectal Cancer Ravia Baldacchini, Lauro Bucchi, Orietta Giuliani, Silvia Mancini, Alessandra Ravaioli, Rosa Vatitato, Paolo Giorgi Rossi, Cinzia Campari, Debra Canuti, Enza Di Felice, Trancesca Mezzetti, Priscilla Sassoli de Bianchi, Stefano Ferretti, and Fabio Falcini, "** on behaff of the Emilia-Romagna Region Workgroup for Colorectal Screening Evaluation "Ongana Cancer Registry, Romagna Cancer Institute, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Turori, RCGS, Meldoia, Fori, Italy, 'Epidemiology Uni, 'Cancer Screening Uni, Azienda Unità Santaria Locale, IRCCS di Regio Scientila, Regio Emila, Italy, 'Cancer Screening Uni, Local Health Authonity, Parament of Heagonan Attinistration, Emilia-Romagna Region, Bologna, Italy, 'University of Ferara and Local Health Authonity, Ferina, Italy, 'Cancer Prevention Uni. Local Health Authonity, Terrin, Italy, 'Department of Heagonan Attinistration, Emilia-Romagna Region, Bologna, Italy, 'University of Ferara and Local Health Authonity, Ferina, Italy, 'Cancer Prevention Uni. Local Health Authonity, Fori, Italy WE ROBIOWE & AMM: We investigated the magnitude and temporal patterns of the decreasing trend in main per- formance measures of fical Immunochenical test (FIT) screening for colorectal cancer (CKC) observed in second and subsequent rounds. MENDIS: We followed up 494,137 participants from the first ratios from multinomial logistic regression models. RESUTS: Between the second and the third round, a significant 20% to 30% decrease was found in the tose form the second round (the first incidence round) using rate ratios from multi- monal colon cancer stabilized by 10% or tes between the second and third rounds.	Results of Compliant Participation in Five Rounds of Fecal Immunochemical Test Screening for Colorectal Cancer Flavia Baldacchini,* Lauro Bucchi,* Orietta Giuliani,* Silvia Mancini,* Alessandra Ravaioli,* Rosa Vattiato,* Paolo Giorgi Rossi,* Cinzia Campari,* Debora Canuti, Enza Di Felice,* Francesca Mezzetti,* Priscilla Sassoli de Bianchi,* Stefano Ferretti,* and Fabio Falcini,*** on behalf of the Emilia-Romagna Region Workgroup for Colorectal Screening Evaluation ************************************		
Results of Compliant Participation in Five Rounds of Fecal Immunochemical Test Screening for Colorectal Cancer Flavia Baldacchini, Lauro Bucchi, Orietta Giuliani, Silvia Mancini, Alessandra Ravaioli, Rosa Vatitato, Paolo Giorgi Rossi, Cinzia Campari, S Debora Canuti, Enza Di Felice, Trancesca Mezzetti, Priscilla Sassoli de Bianchi, S Stefano Ferretti, and Fabio Falcini, "** on behaff of the Emilia-Romagna Region Workgroup for Colorectal Screening Evaluation "Pongana Cancer Registry, Romagna Cancer Institute, Istituto Scientifico Romagnio per lo Studio e la Cura dei Turori, IRCES, Meldola, Fori, Italy, 'Epidemiology Uni, 'Cancer Screening Uni, Azienda Unità Sanitaria Locale, IRCES di Regio Cancer Prevention Uni, Local Health Authority, Fori, Italy 'Cancer Prevention Uni, Local Health Authority, Fori, Italy WE followed up 494,187 participants from the first round of a regional biennial FT screening program in Italy (Cut-off value for positivity, 20 g hemoglobing feces) for 5 total rounds (2005-2016). At each round, only compliant participants were eligible. Parformance measures of fecal immunochemical test (FT) screening for colorectal cancer (CRC) observed in second and the third round, a regional Diemai TT screening program in Italy (Cut-off value for positivity, 20 ag hemoglobing feces) for 5 total rounds (2005-2016). At each round, only compliant participants were eligible. RESULTS: Between the second and the third round, a significant 20% to 30% decrease was found in the torsporthon of me with a positive Trassut (from 5.2% to 4.3%) a	Results of Compliant Participation in Five Rounds of Fecal Immunochemical Test Screening for Colorectal Cancer Flavia Baldacchini,* Lauro Bucchi,* Orietta Giuliani,* Silvia Mancini,* Alessandra Ravaioli,* Rosa Vattiato,* Paolo Giorgi Rossi,* Cinzia Campari,* Debora Canuti, Enza Di Felice,* Francesca Mezzetti,* Priscilla Sassoli de Bianchi,* Stefano Ferretti,* and Fabio Falcini,**** on behalf of the Emilia-Romagna Region Workgroup for Colorectal Screening Evaluation "romagne Cancer Registry, Romagne Cancer Institute, Stituto Scientifico Romagnelo per lo Studie e la Cura dei Turori, ItrOCS, Meldola, Forti, Italy: "Epidemiology Unit, 'Cancer Screening Unit, Local Health Authority, Ternini, Italy: "Deartment of Health Regional Administation, Emilia, Hegi, 'Cancer Screening Unit, Local Health Authority, Fornini, Italy: "Cancer Prevention Unit, Local Health Authority, Fornini, Italy: "Cancer Prevention Unit, Local Health Authority, Forsitiuty, 20, a phemoglobing feecis) for 5 total rounds (2005-2016), At each round, only compliant participants were eligible. Performance measures of fecal immunochemical test (FT) screening plorgamered with those from the second round (the first, thrich, forth, and fifth round were compared with those from the second round (the first, thrich, forth, and fifth round were compared with toos from the second and the third round, a significant 20% to 30% decrease was found in the proportion of men with a positive FT result (from 5.2% to 4.3%) and in detection rates of advanced aeomagned (from 15.1 to 11.6 per 1000), Positive predictive values (PPV) decrease durated there on advanced aeomagned from 15.1 to 11.6 per 1000, Positive predictive values (PPV) decrease durated find rounds. The CPVs for advanced adeomagned f		
ENERGY Control of the second and the third round, a significant 20% to 33% decrease was found in the proportion of men with a positive FIT result (from 5.2% to 4.3%) and in detection rates of decrease display in the fourth and fifth rounds. The detection rates of decrease display in the fourth and fifth rounds. The detection rates of decimation and fifth rounds. The PPVS for a decrease display in the fourth and fifth rounds. The PPVS for a decrease display in the result of the second round, but the fourth round in the round and fifth rounds. The PPVS for a decrease display in the fourth and fifth rounds. The detection rates of decimation and the fifth rounds. The PPVS for a decrease display in the fourth and fifth rounds. The detection rates of decimation decimation form and the fifth rounds. METHODS: We followed up 494.187 participants from the first round of a regional biennial FIT screening for colorectal cancer (RCG) observed in second and the third round, a significant 20% to 33% decrease was found in the genesion and the decrease in the decrease in the decrease of	Immunochemical Test Screening for Colorectal Cancer Flavia Baldacchini,* Lauro Bucchi,* Orietta Giuliani,* Silvia Mancini,* Alessandra Ravaioli,* Rosa Vattitato,* Paolo Giorgi Rossi,* Cinzia Campari,* Debora Canuti, IEnza Di Felice,* Francesca Mezzetti,* Priscilla Sassoli de Bianchi,* Stefano Ferretti,* and Fabio Falcini,*** on behalf of the Emilia-Romagna Region Workgroup for Colorectal Screening Evaluation "Romagna Cancer Registry, Romagna Cancer Institute, Stituto Scientifico Romagnelo per lo Studio e la Cura dei Turnori, IRCCS, Meldoia, Fori, Italy: "Epidemiology Unit, "Cancer Screening Unit, Local Health Authority, Thimi, Italy: "Department of Health, Regional Administration, Emilia, Hago: Teochericology Unit, Coard Health Authority, Thimi, Italy: "Department of Health Regional Administration, Emilia, Hago: Teochericology Unit, Local Health Authority, Thimi, Italy: "Department of Health Regional Administration, Emilia, Tagy: "Cancer Prevention Unit, Local Health Authority, Forin, Italy BACKGROUND & AIMS: We investigated the magnitude and temporal patterns of the decreasing trend in main performance measures of facal Immunochemical test (FT) screening for colorectal cancer (CRC) observed in second round (the first incidence round) using rate ratios from multivariate Poisson regression models and relative risk ratios from multivariate Poisson regression models and relative risk ratios from multivariate Poisson (rom 15:1 to 11.6 Je per 1000), RCR (Cm 17:1 to 14.9 per 1000), and advanced anepalasi (from 15:1 to 11.6 Je per 1000), RCR (Cm 17:1 to 14.9 per 1000), and advanced menpalasi (Cm 15:1 to 11.6 per 1000). Positive predictive values (PPVs) for adenoma stabilized by the fourth and fi	Results of Co	ompliant Participation in Five Rounds of Fecal
Flavia Baldacchini,* Lauro Bucchi,* Orietta Giuliani,* Silvia Mancini,* Alessandra Ravaioli,* Rosa Vattiato,* Paolo Giorgi Rossi,* Cinzia Campari,* Debora Canuti, I Enza Di Felice,* Francesca Mezzetti,* Priscilla Sassoli de Bianchi,* Stefano Ferretti,* and Fabio Falcini,*** on behalf of the Emilia-Romagna Region Workgroup for Colorectal Screening Evaluation * * Formagna Cancer Registry, Romagna Cancer Institute, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Turnori, IRCCS, Meldola, Fori, Italy,* * * * * Teomagna Cancer Registry, Romagna Cancer Institute, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Turnori, IRCCS, Meldola, Fori, Italy,* * * * * * * * <td< td=""><td>Flavia Baldacchini,* Lauro Bucchi,* Orietta Giuliani,* Silvia Mancini,* Alessandra Ravaioli,* Rosa Vattiato,* Paolo Giorgi Rossi,* Cinzia Campari,* Debora Canuti, Enza Di Felice,* Francesca Mezzetti,* Priscilla Sassoli de Bianchi,* Stefano Ferretti,* and Fabio Falcini,*** on behalf of the Emilia-Romagna Region Workgroup for Colorectal Screening Evaluation *** *** Gancer Institute, Istitute Scientifico Romagnelo per lo Studio e la Cura dei Tumori, IRCCS, Meldola, Fori, Italy, 'Epidemiology Uni, *Cancer Screening Unit, Azienda Unité Sanitaria Locale, IRCCS di Reggio Emilia, Reggio Emilia, Italy, 'Cancer Screening Unit, Azienda Unité Sanitaria Locale, IRCCS di Reggio Emilia, Reggio Emilia, Italy, 'Cancer Screening Unit, Local Health Authority, Finnin, Italy, 'Department of Health, Reggional Administration, Emilia-Romagna Region, Bologna, Italy, 'University of Fernara and Local Health Authority, Fernar, Italy, 'Cancer Prevention Unit, Local Health Authority, Finni, Italy BACKGROUND & AIMS: We investigated the magnitude and temporal patterns of the decreasing trend in main per- formance measures of fecal immunochemical test (FT) screening for colorectal cancer (CRC) observed in second round (the first incidence round) using rate ratios from multi- variate Poisson regression models and relative risk ratios from multi- variate Poisson regression models and relative risk ratios from multi- variate Poisson regression models and relative risk ratios from multi- variate Poisson regression models and relative risk ratios from multinomial logistic regression models. RESULTS: Between the second and the third round, a significant 20% to 30% decrease was found in the proportion of men</td><td>Immunochen</td><td>nical Test Screening for Colorectal Cancer</td></td<>	Flavia Baldacchini,* Lauro Bucchi,* Orietta Giuliani,* Silvia Mancini,* Alessandra Ravaioli,* Rosa Vattiato,* Paolo Giorgi Rossi,* Cinzia Campari,* Debora Canuti, Enza Di Felice,* Francesca Mezzetti,* Priscilla Sassoli de Bianchi,* Stefano Ferretti,* and Fabio Falcini,*** on behalf of the Emilia-Romagna Region Workgroup for Colorectal Screening Evaluation *** *** Gancer Institute, Istitute Scientifico Romagnelo per lo Studio e la Cura dei Tumori, IRCCS, Meldola, Fori, Italy, 'Epidemiology Uni, *Cancer Screening Unit, Azienda Unité Sanitaria Locale, IRCCS di Reggio Emilia, Reggio Emilia, Italy, 'Cancer Screening Unit, Azienda Unité Sanitaria Locale, IRCCS di Reggio Emilia, Reggio Emilia, Italy, 'Cancer Screening Unit, Local Health Authority, Finnin, Italy, 'Department of Health, Reggional Administration, Emilia-Romagna Region, Bologna, Italy, 'University of Fernara and Local Health Authority, Fernar, Italy, 'Cancer Prevention Unit, Local Health Authority, Finni, Italy BACKGROUND & AIMS: We investigated the magnitude and temporal patterns of the decreasing trend in main per- formance measures of fecal immunochemical test (FT) screening for colorectal cancer (CRC) observed in second round (the first incidence round) using rate ratios from multi- variate Poisson regression models and relative risk ratios from multi- variate Poisson regression models and relative risk ratios from multi- variate Poisson regression models and relative risk ratios from multi- variate Poisson regression models and relative risk ratios from multinomial logistic regression models. RESULTS: Between the second and the third round, a significant 20% to 30% decrease was found in the proportion of men	Immunochen	nical Test Screening for Colorectal Cancer
Alessandra Ravaioli, * Rosa Vattiato, * Paolo Giorgi Rossi, * Cinzia Campari, * Debora Canuti, * Enza Di Felice, * Francesca Mezzetti, * Priscilla Sassoli de Bianchi, * Stefano Ferretti, * and Fabio Falcini, *** on behalf of the Emilia-Romagna Region Workgroup for Colorectal Screening Evaluation ****	Alessandra Ravaioli,* Rosa Vattiato,* Paolo Giorgi Rossi,* Cinzia Campari,* Debora Canuti, "Enza Di Felice,* Francesca Mezzetti,* Priscilla Sassoli de Bianchi,* Stefano Ferretti,* and Fabio Falcini,*** on behalf of the Emilia-Romagna Region Workgroup for Colorectal Screening Evaluation ''romagna Cancer Registry, Romagna Cancer Institute, letituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, IrCOS, Melcola, Fordi, Italy,* Epidemology Unit, *Cancer Screening Unit, Azienda Unita Sanitaria Locale, IRCOS el Reggio Emilia, Regional Administration, Emilie Aleggio Cancer Screening Unit, Local Health Authority, Ferri, Italy,* "University of Ferrara and Local Health Authority, Ferrara, Italy; *Cancer Prevention Unit, Local Health Authority, Fordi, Italy BACKGROUND & AIMS: BACKGROUND & AIMS: We investigated the magnitude and temporal patterns of the decreasing trend in main performance measures of fecal immunochemical test (FIT) screening for colorectal cancer (CRC) observed in second round (Lefos-2016). At each round, only complaint participants from multinomial logistic regression models. METHODS: We followed up 494.187 participants from the first round of a regional biennial FIT screening program in Italy (cut-off value for positivity, 20 g hemoglobin/g feces) for 5 total rounds (2005-2016). At each round, only complaint participants from multinomial logistic regression models. RESULTS: We followed up 494.187 participants from the first round of a regional biennial from the forst the indence on pais from Tist to 11.6 per 1000). Positive predictive values (PPVs) decrease was found in the proforion of men with a positive FIT result (from 5.2% to 4.3%)	Flavia Baldacchir	ni.* Lauro Bucchi.* Orietta Giuliani.* Silvia Mancini.*
Debora Canuti, ^I Enza Di Felice, [¶] Francesca Mezzetti, [¶] Priscilla Sassoli de Bianchi, [¶] Stefano Ferretti, [#] and Fabio Falcini, ^{***} on behalf of the Emilia-Romagna Region "Romagna Cancer Registry, Romagna Cancer Institute, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Turnoi, IRCCS, Meldola, Forli, Italy, [*] Epidemiology Unit, [*] Cancer Screening Unit, Azienda Unita Sanitaria Local, IRCCS di Registo Finilia, Regio Emilia, Italy, [*] Cancer Screening Unit, Local Health Authority, Rimini, Italy, [*] Department of Health, Regional Administration, Emilia-Romagna Region, Bologna, Italy, [*] University of Ferara and Local Health Authority, Ferrar, Italy, ^{**} Cancer Prevention Unit, Local Health Authority, Forli, Italy BACKGROUND & AIMS: We investigated the magnitude and temporal patterns of the decreasing trend in main performance measures of facal Immunochemical test (FIT) screening for colorectal cancer (CKC) observed in second and subservend in second and subservend in second and subservend in second and the first, third, fourth, and fifth round were compared with those from the second and the third round, a significant 20% to 30% decrease was found in the proportion of me with a positive FIT result (from 5.2% to 4.3%) and in detection rates on advanced adenoma (from 13.4 to 10.2 per 1000), CRC (from 1.7 to 1.4 per 1000), and advanced neoplasia (from 15.4 to 11.6 per 1000), Positive FIT result (from 0.7% to 3.9% decrease was found in the proximal color cancer stabilized after the second round, whereas the detection rate of distal CRC decreased until the fourth round in men (from 0.7 to 0.3 per 1000), and the fifth round in women. CONCLUSIONE: These findings support the notion that FIT screening prevents progression of a subset of advanced adenomas. Screening intensity could be modulated based on res	Debora Canuti, ^I Enza Di Felice, [¶] Francesca Mezzetti, [¶] Priscilla Sassoli de Blanchi, [¶] Stefano Ferretti, [#] and Fabio Falcini, on behalf of the Emilia-Romagna Region Workgroup for Colorectal Screening Evaluation [#] Romagna Cancer Registry, Romagna Cancer Institute, Isituto Scientifico Romagnolo per lo Studio e la Cura dei Turnoi, IRCCS, Meldon, Forti, Iaty, [*] Epidemiology Unit, ⁵ Cancer Screening Unit, Azienda Unità Sanitaria Local, IRCCS di Regigi Emilia, Reggio Emilia, Italy, [*] Cancer Screening Unit, Local Health Authority, Rimini, Italy, [*] Department of Health, Regional Administration, Emilia-Formagna Region, Bologna, Italy, [*] University of Ferrara and Local Health Authority, Ferrara, Italy; ^{**} Cancer Prevention Unit, Local Health Authority, Forti, Italy BACKGROUND & AIMS: We investigated the magnitude and temporal patterns of the decreasing trend in main per- formance measures of fecal immunochemical test (FIT) screening for colorectal cancer (CRC) observed in second and subsequent rounds. METHODS: We followed up 494,187 participants from the first round of a regional biennial FIT screening program in Italy (cut-off value for positivity, 20 µg hemoglobin/g fecces) for 5 total rounds (2005-2016). At each round, only compliant participants were eligible. Performance measures for the first, Inif, fourth, and fifth round were compared with those from the second round (the first incidence round) using rate ratios from multi- variate Poisson regression models and relative risk ratios from multinomial logistic regression models. RESULTS: Between the second and the third round, a significant 20% to 30% decrease was found in the proportion of men with a positive FIT result (from 5.2% to 4.3%) and in detection rates of advanced adenoma, CRC and at to 10.2 per 1000), RC (from 1.7 to 1.4 per 1000), and the fifth round is women. CONCLUSIONS: These findings support the notion that FIT screening prevents progression of a subset of advanced adenomas. Screening intensity could be modulated based on r	Alessandra Rava	oli,* Rosa Vattiato,* Paolo Giorgi Rossi, [‡] Cinzia Campari, [§]
Stefano Ferretti, # and Fabio Falcini, *** on behalf of the Emilia-Romagna Region Workgroup for Colorectal Screening Evaluation *Romagna Cancer Registy, Romagna Cancer Institute, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Turnori, IRCCS, Meldola, Fori, Itay; "Epidemiology Unit, "Cancer Screening Unit, Azienda Unita Santina Locale, IRCCS di Regional Administration, Emilia-Romagna Region, Bologna, Italy; "University of Ferrara and Local Health Authority, Ferrara, Italy; "Cancer Screening Unit, Local Health Authority, Ferrara, Italy; "Cancer Screening Unit, Local Health Authority, Ferrara, Italy; "Cancer Screening Unit, Local Health Authority, Fori, Italy BACKGROUND & AIMS: We Investigated the magnitude and temporal patterns of the decreasing trend in main performance measures of fecal immunochemical test (FIT) screening for colorectal cancer (CRC) observed in second and subsequent rounds. METHODS: We followed up 494,187 participants from the first round of a regional biennial FT screening program in Italy (cu-off value for positivity, 20 µg hemoglobin/g feces) for 5 total rounds (2005-2016). At each round, only compliant participants were eligible. Performance measures from the first, third, fourth, and fifth round were compared with those from the second round (the first incidence round) using rate ratios from multivariate Poisson regression models and relative risk ratios from multinomial logistic regression models. RESULTS: Between the second and the third round, a significant 20% to 30% decrease was found in the orpolasi (from 13.4 to 10.2 per 1000), CRC (from 1.7 to 1.4 per 1000), and davanced neoplasa (from 13.4 to 10.2 per 1000, CRC (from 1.7 to 1.4 per 1000), and davanced neoplasa (from 15.4 to 11.6 per 1000). Positive predictive values (PPVs) decr	Stefano Ferretti, [#] and Fabio Falcini, *** on behalf of the Emilia-Romagna Region Workgroup for Colorectal Screening Evaluation *Romagna Cancer Registy, Romagna Cancer Institute, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Turnori, IRCOS, Meldola, Fori, Italy: "Epidemiology Unit, "Cancer Screening Unit, Lozel Health Authority, Finni, Ray, "Department of Health, Regional Administration, Emilia-Romagna Region, Bologna, Italy," University of Perara and Local Health Authority, Ferrara, Italy, "Cancer Prevention Unit, Local Health Authority, Fori, Italy BACKGROUND & AIMS: We investigated the magnitude and temporal patterns of the decreasing trend in main performance measures of fecal immunochemical test (FIT) screening for colorectal cancer (CRC) observed in second and subsequent rounds. METHODS: We followed up 494,187 participants from the first round of a regional biennial FIT screening program in Italy (cut-off value for positivity, 20 µg hemoglobin/g feces) for 5 total rounds (2005-2016). At each round, only compliant participants were eligible. Performance measures for the first, Iniri, fourth, and fifth round vere compared with those from the second round (the first incidence round) using rate ratios from multivariate Poisson regression models and relative risk ratios from multinomial logistic regression models. RESULTS: Between the second and the third round, a significant 20% to 30% decrease was found in the proportion of men with a positive FIT result (from 5.2% to 4.3%) and in detection rates of advanced adenoma (from 13.4 to 10.2 per 1000), CRC (from 17 to 1.4 per 1000), and advanced neoplasia (from 15.1 to 11.6 per 1000), Positive predictive values (PPVs) decreased by 10% or previmal color cancer stabilbized after the second nomod, whereas the d	Debora Canuti. E	Enza Di Felice. ¹ Francesca Mezzetti. ¹ Priscilla Sassoli de Bianchi. ¹
 Workgroup for Colorectal Screening Evaluation "Romagna Cancer Registry, Romagna Cancer Institute, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Turnori, IRCCS, Meldola, Fori, Italy; "Epidemiology Unit, "Cancer Screening Unit, Azienda Unità Sanitaria Locale, IRCCS di Reggio Emilia, Italy, "Cancer Screening Unit, Local Health Authority, Filmini, Italy; "Department of Health, Regional Administration, Emilia-Romagna Region, Bologna, Italy; "University of Ferrara and Local Health Authority, Ferrara, Italy; "Cancer Prevention Unit, Local Health Authority, Fori, Italy; BACKGROUND & AIMS: We investigated the magnitude and temporal patterns of the decreasing trend in main performance measures of fecal immunochemical test (FIT) screening for colorectal cancer (CRC) observed in second and subsequent rounds. METHODS: We followed up 494,187 participants from the first round of a regional biennial FIT screening program in Italy (cut-off value for positivity, 20 µg hemoglobin/g feces) for 5 total rounds (2005-2016). At each round, only compliant participants were eligible. Performance measures from the first third, fourth, and fifth round were compared with those from the second round (the first incidence round) using rate ratios from multivariate Poisson regression models and relative risk ratios from multivariate Poisson regression models and relative risk ratios from multinomial logistic regression models. RESULTS: Between the second and the third round, a significant 20% to 30% decrease was found in the proportion of men with a positive FIT result (from 5.2% to 4.3%) and in detection rates of advanced adeoma (from 15.1 to 11.6 per 1000). Positive predictive values (PPVs) decreased by 10% or less between the second round, the fourth round, whereas the detection rate of proximal colon cancer stabilized fiter the second round, whereas the detection rate of oprixima colon cancer stabilized fiter the second round, whereas the detection rate of proxim	Workgroup for Colorectal Screening Evaluation "Romagna Cancer Registry, Romagna Cancer Institute, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Turnori, IRCCS, Meldola, Fori, Italy, "Egnidemiology Unit, "Cancer Screening Unit, Azienda Unită Santinia Locale, IRCCS di Reggio Emilia, Reggio Emilia, Italy, "Cancer Screening Unit, Local Health Authority, Remara, Italy, "Cancer Prevention Unit, Local Health Authority, Forii, Italy BACKGROUND & AIMS: We investigated the magnitude and temporal patterns of the decreasing trend in main per- formance measures of fecal immunochemical test (FIT) screening for colorectal cancer (CRC) observed in second and subsequent rounds. METHODS: We followed up 494,187 participants from the first round of a regional biennial FIT screening program in Italy (cut-off value for positivity, 20 gg hemoglobin/g feces) for 5 total rounds (2005-2016). At each round, only compliant participants were eligible. Performance measures from the first, third, fourth, and fifth round were compared with those from the second round (the first incidence round) using rate ratios from multi- variate Poisson regression models and relative risk ratios from multi- variate Poisson regression models and relative risk ratios from multi- variate Poisson regression models and relative risk ratios from multi- variate Poisson regression models. RESULTS: Between the second and the third round, a significant 20% to 30% decrease was found in the proportion of men with a positive FIT result (from 5.2% to 4.3%) and in detection rate of advanced adenoma (from 13.4 to 10.2 per 1000), RC (from 1.7 to 1.4 per 1000), and davanced neoplasia (from 15.1 to 11.6 per 1000). Positive predictive values (PPV) decreased by 10% or less between the second and third rounds. Detection rates and PPVs for adenoma stabilized	Stefano Ferretti.#	and Fabio Falcini.*** on behalf of the Emilia-Romagna Region
 ¹Romagna Cancer Registry, Romagna Cancer Institute, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Turnori, IRCCS, Mieldola, Fori, Italy, "Epidemiology Unit, "Local Health Authority, Rimini, Italy," Department of Health, Regional Administration, Emilia-Amagna Region, Bologna, Italy," University of Ferrara and Local Health Authority, Ferrara, Italy; "Cancer Prevention Unit, Local Health Authority, Fori, Italy BACKGROUND & AIMS: We investigated the magnitude and temporal patterns of the decreasing trend in main performance measures of fecal immunochemical test (FIT) screening for colorectal cancer (CRC) observed in second and subsequent rounds. METHODS: We followed up 494,187 participants from the first round of a regional biennial FIT screening program in Italy (cut-off value for positivity, 20 µg hemoglobin/g feces) for 5 total rounds (2005-2016). At each round, only compliant participants were eligible. Performance measures from the first, third, fourth, and fifth round were compared with those from the second round (the first incidence round) using rate ratios from multi-variate Poisson regression models and relative risk ratios from multinomial logistic regression models. RESULTS: Between the second and the third round, a significant 20% to 30% decrease was found in the proportion of men with a positive FIT result (from 5.2% to 4.3%) and in detection rates of advanced adenoma (from 13.1 to 11.6 per 1000). Positive predictive values (PPVs) decreased by 10% or less between the second and third rounds. Detection rates and PPVs for adavanced neoplasia decreased slightly in men and women by the fourth and fifth rounds. The PPVs for advanced neoplasia decreased slightly in men and women by the fourth and fifth round in women. CONCLUSIONS: These findings support the notion that FIT screening prevents progression of a subset of advanced adenomas. Screening intensity could be modulated based on results from previous rounds, with a risk-bas	 "Romagne Cancer Registry, Romagne Cancer Institute, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Turnori, IRCCS, Meldos, Forli, Italy, "Epidemiology Unit, Cancer Screening Unit, Azienda Unità Sanitaria Locale, IRCCS di Regigio Emilia, Regio Emilia, Italy, "Cancer Screening Unit, Local Health Authority, Firrara, Italy; "Cancer Prevention Unit, Local Health Authority, Forli, Italy BACKGROUND & AIMS: We investigated the magnitude and temporal patterns of the decreasing trend in main performance measures of fecal immunochemical test (FIT) screening for colorectal cancer (CRC) observed in second and subsequent rounds. METHODS: We followed up 494,187 participants from the first round of a regional biennial FIT screening program in Italy (cut-off value for positivity, 20 µg hemoglobin/g feces) for 5 total rounds (2005-2016). At each round, only compliant participants were eligible. Performance measures from the first, third, fourth, and fifth round were compared with those from the second round (the first incidence round) using rate ratios from multivariate Poisson regression models and relative risk ratios from multinomial logistic regression models. RESULTS: Between the second and the third round, a significant 20% to 30% decrease was found in the proportion of men with a positive FIT result (from 5.2% to 4.3%) and in detection rates of advanced adenoma (from 13.4 to 10.2 per 1000), CRC (from 1.7 to 1.4 per 1000), and dvanced neoplasia (from 15.1 to 11.6 per 1000). Positive predictive values (PPV) decreased by 10% or less between the second and third rounds. Detection rates and PPVs for adenoma stabilized by the fourth and fifth rounds. The PPVs for adenoma stabilized by the fourth and fifth rounds. The PPVs for adenoma stabilized by the fourth and fifth rounds. The PPVs for adenoma stabilized by the fourth and fifth rounds. The PPVs for adenoma stabilized by the fourth and fifth rounds. The detection rate of distal CRC decrease allot and results from	Workgroup for C	olorectal Screening Evaluation
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Abbreviations used in this paper: CRC, colorectal cancer; DR, detection rate; FIT, fecal immunochemical test; PPV, positive predictive value.

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117 However, it is unclear whether the decrease con-118 tinues for certain performance measures after the second 119 round. This depends, first, on the varying design of the 120 **Q14** relevant studies. In general, the authors defined a 121 screening round as a complete cycle of invitations, during which the whole target population was invited.^{1–5,8} 122 123 Under this design, all participants in any given round 124 were evaluated irrespective of their participation in 125 previous rounds. For example, subjects who responded 126 to an invitation after 2 refusals contributed to the results 127 of the third screening round, although they were actually 128 at their prevalence round. In 2 studies, conversely, only 129 subjects with compliant participation to previous rounds 130 were considered eligible.^{6,7} Subjects participating in the third round, for example, were eligible only if they also 131 132 had participated in the first 2 rounds.

Second, most studies had a small size and covered 133 134 limited observation times. Some studies considered only 135 the first 2 rounds.^{2,5} In a study covering 6 rounds, the proportion of positive FIT results, the detection rate (DR) 136 137 of advanced adenoma, and the PPV for advanced ade-138 noma decreased between the first and the second round, 139 and then stabilized. The DR of CRC, instead, continued to 140 decrease, with a DR ratio of the sixth round to the first 141 round as low as 0.18.7

142 Third, most previous studies did not make an allow-143 ance for the aging of the population, which is associated with increasing risk of disease. This explains, for 144 145 example, the increase in the proportion of positive FIT 146 results and the DR of advanced neoplasia that was 147 observed at the fourth round of a screening trial.⁸

148 **Q15** This article describes a large study of this issue. which aimed to evaluate the performance of compliant participation in the first 5 rounds of a biennial FIT screening program in Italy.

Materials and Methods

Setting

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In the Emilia-Romagna Region (northern Italy), a 158 population-based CRC screening program has been 159 ongoing since March 2005. The target population in-160 cludes the residents of both sexes ages 50 to 69 years 161 (n = 1,037,532 on January 1, 2005). The program is run 162 at the health care district level (n = 11) according to a 163 standard protocol. 164

Every 2 years, eligible subjects are invited with a 165 personal letter to perform a single-sample FIT. Most kits 166 are distributed by public pharmacies and primary care 167 facilities.⁹ Nonresponders to the invitation are mailed a 168 reminder, usually within 6 months. The screening test is 169 a latex agglutination test (OC-Sensor: Eiken Chemical Co. 170 Tokyo, Japan) without dietary restrictions. The cut-off 171 value for positivity is 20 μ g hemoglobin/g feces (100 172 ng hemoglobin/mL of buffer). Subjects are notified of 173 negative FIT results by mail. Subjects with positive 174

what you need to know
Background
Little is known about the magnitude and temporal patterns of the decreasing trends in main perfor- mance measures of fecal immunochemical test (FIT) screening for colorectal cancer that have been observed in second and subsequent rounds.
Findings

Findings

Findings from the study support the concept that FIT screening prevents progression of a subset of advanced adenomas. Screening intensity could be modulated based on results from previous rounds, with a risk-based strategy.

Implications for patient care

FIT screening strategies for colorectal cancer might be designed specifically for each patient based on results from previous rounds of screening.

results are contacted by telephone, invited to attend a screening center, and referred for complete conventional colonoscopy under sedation. In the case of incomplete colonoscopy, patients are presented with the option of a Q16 virtual colonoscopy. Patients with positive FIT results and a negative colonoscopic assessment are re-invited to a FIT screening 5 years later.

Objectives and Design

The study had a cohort design. The objectives were to contrast the performance measures of FIT screening at each of the first 5 rounds in a population of compliant participants with the average measures observed in the total screening population, and to investigate the decrease observed among compliant participants by comparing the third, fourth, and fifth round with the second round (ie, the first incidence round).

215 Regarding compliant participants, the performance 216 measures were calculated cross-sectionally, for 5 rounds, in a cohort of subjects including all residents ages 50 to 217 69 years who were invited and had a FIT during the first 218 round of the screening program. The dates of FITs varied 219 between March 21, 2005, and December 31, 2016. A 220 compliant participant was defined as one who had 2, 3, 4, 221 or 5 consecutive FITs at standard intervals (ie, 2 y \pm 6 2.2.2 223 mo). The follow-up evaluation of each FIT ceased on the date of the following events, whichever came first: last 224 regular FIT; receipt of colonoscopy for a positive FIT 225 result; screening cessation (at age 70 y); migration; and 226 death. Colonoscopies performed within 1 year of a pos-227 itive FIT result and surgical treatments performed within 228 229 1 year of a positive colonoscopy were considered part of 230 a single screening episode. The last date of follow-up evaluation of positive FIT results was December 231 31, 2018. 232

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Results of 5 Rounds of FIT Screening 3

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Table 1. Total Screening Population: Number of Subjects Invited to and Participating in Five Organizational Screening Rounds, the Number of Subjects With Positive FIT Results, of Subjects Undergoing Colonoscopic Assessment, of Subjects With Successful Cecal Intubation, and of Subjects Diagnosed With Colorectal Adenoma and Colorectal Cancer, by Sex and Screening Round

	Males					Females				
	1st	2nd	3rd	4th	5th	1st	2nd	3rd	4th	5th
Invited	405,639	477,656	489,301	521,819	525,698	439,466	512,661	529,538	562,309	565,873
Participating	183,503	229,254	244,577	258,001	261,179	214,941	266,779	283,270	299,020	302,663
With positive FIT results	13,108	14,397	12,170	12,140	13,370	9974	11,491	10,176	10,505	11,893
With colonoscopic assessment	10,397	11,496	9967	9840	10,624	7586	8792	8188	8379	9301
With successful cecal intubation	9853	11,053	9445	9487	10,289	7015	8382	7732	8100	8969
With adenoma										
Advanced adenoma	4062	3729	3218	3063	2930	2160	2046	1843	1786	1754
Total adenoma	5668	5907	5014	4710	4784	3082	3296	3000	2835	2899
With colorectal cancer ^a										
Stage I	383	313	198	152	139	252	188	126	115	109
Stage II	136	90	81	59	48	73	66	62	46	47
Stage III	145	119	66	72	53	98	88	69	72	51
Stage IV ^a	NA	5	9	12	11	NA	2	8	7	4
Stage unknown	191	69	55	41	59	89	35	36	27	28
Total colorectal cancer	855	596	409	336	310	512	379	301	267	239
With advanced neoplasia ^b	4917	4325	3627	3399	3240	2672	2425	2144	2053	1993

NOTE. All data are from the Emilia-Romagna Region colorectal cancer screening program (2005-2014).

FIT, fecal immunochemical test; NA, not available.

^aDuring the first screening round, data for stage IV colorectal cancer in the total screening population were not collected.

^bAdvanced neoplasia indicates advanced adenoma and colorectal cancer.

With respect to the total screening population, the performance measures of screening were calculated in five 2-year screening rounds (organizational rounds). The population was treated as an open cohort.

Data Sources

With respect to the total screening population, study data were taken from the annual national surveys conducted by the National Centre for Screening Monitoring, which collects standard data from local screening units. Data on the detection of CRC by disease site were not collected.

273 Data for compliant participants were obtained from 274 the Information System for the Surveillance of Colorectal 275 Screening (flusso informativo Screening Colon-Retto) of 276 the Department of Health of the Regional Administration. 277 Every 4 months, each health care district screening unit 278 provides electronic records for all subjects in the target 279 population. The System is an anonymous relational 280 database created by record-linking multiple data sets 281 (population list, invitations, FITs, colonoscopies, di-282 agnoses, surgical treatments, and vital status). The find-283 ings of each screening episode are classified as follows: CRC, advanced adenoma (≥ 1 cm in diameter, or villous/ 284 285 tubulovillous type, or with high-grade dysplasia), non-286 advanced adenoma, or negative. In the case of CRC, tu-287 mor stage and disease site were recorded. Tumor stage 288 was classified according to the American Joint Committee on Cancer TNM staging system, sixth edition. Disease site 289 290 was classified as the proximal colon (from the cecum to

the transverse colon), distal colon (from the splenic flexure to the sigmoid colon), and rectum (rectosigmoid junction and rectum).¹⁰ Because a successful cecal intubation was achieved in a proportion of patients close to 100%, this information was not included in the download file.

Performance Measures

The primary study end points included the following performance measures: (1) the proportion of positive FIT results (ie, the percentage of subjects with a completed FIT who had a positive result); (2) the DR of advanced adenoma, CRC, and advanced neoplasia (including CRC and advanced adenoma) (ie, the proportion of subjects with a completed FIT who were diagnosed with these lesions per 1000 screenees); and (3) the PPV for adenoma (also referred to as the adenoma detection rate),¹¹ advanced adenoma, CRC, and advanced neoplasia at colonoscopy (ie, the percentage of subjects undergoing colonoscopy who were diagnosed with nonadvanced/advanced adenoma, advanced adenoma, CRC, and advanced neoplasia).

Statistical Analysis

Analysis was truncated at the fifth screening round 345 because the length of follow-up evaluation available in 346 the case of positive FIT results in the sixth round was 347 insufficient for more than 50% of subjects. 348

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Table 2. Total Screening Population: Participation Rate, Proportion of Positive FIT Results, Colonoscopic Assessment Rate,

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	Males					Females				
	1st	2nd	3rd	4th	5th	1st	2nd	3rd	4th	5th
Participation rate, %	45.2	48.0	50.0	49.4	49.7	48.9	52.0	53.5	53.2	53.5
Proportion of positive FIT results, %	7.1	6.3	5.0	4.7	5.1	4.6	4.3	3.6	3.5	3.9
Colonoscopic assessment rate, %	79.3	79.8	81.9	81.1	79.5	76.1	76.5	80.5	79.8	78.2
Successful cecal intubation rate, %	94.8	96.1	94.8	96.4	96.8	92.5	95.3	94.4	96.7	96.4
DR of advanced adenoma (per 1000)	22.1	16.3	13.2	11.9	11.2	10.0	7.7	6.5	6.0	5.8
DR of colorectal cancer (per 1000)	4.7	2.6	1.7	1.3	1.2	2.4	1.4	1.1	0.9	0.8
DR of advanced neoplasia ^a (per 1000)	26.8	18.9	14.8	13.2	12.4	12.4	9.1	7.6	6.9	6.6
PPV for adenoma, ^b %	54.5	51.4	50.3	47.9	45.0	40.6	37.5	36.6	33.8	31.2
PPV for advanced adenoma, %	39.1	32.4	32.3	31.1	27.6	28.5	23.3	22.5	21.3	18.9
PPV for colorectal cancer, %	8.2	5.2	4.1	3.4	2.9	6.7	4.3	3.7	3.2	2.6
PPV for advanced neoplasia, %	47.3	37.6	36.4	34.5	30.5	35.2	27.6	26.2	24.5	21.4
DR of stage I colorectal cancer (per 1000)	2.1	1.4	0.8	0.6	0.5	1.2	0.7	0.4	0.4	0.4
DR of stage II colorectal cancer (per 1000)	0.7	0.4	0.3	0.2	0.2	0.3	0.2	0.2	0.2	0.2
DR of stage III colorectal cancer (per 1000)	0.8	0.5	0.3	0.3	0.2	0.5	0.3	0.2	0.2	0.2
DR of stage IV colorectal cancer (per 1000) ^c	NA	<0.1	<0.1	<0.1	<0.1	NA	<0.1	<0.1	<0.1	<0.

369 NOTE. All data are from the Emilia-Romagna Region colorectal cancer screening program (2005-2014). The participation rate is per 100 subjects invited. The 370 proportion of positive FIT results is per 100 subjects undergoing FIT screening. The colonoscopic assessment rate is per 100 subjects with positive FIT results. The 371 successful cecal intubation rate is per 100 subjects with positive FIT results undergoing colonoscopic assessment. The DRs of advanced adenoma, colorectal 372 cancer, and advanced neoplasia are per 1000 subjects undergoing FIT screening. The PPVs are per 100 subjects with positive FIT results undergoing colonoscopic assessment. Anal cancer cases were excluded from the DR of colorectal cancer by tumor stage. 373

DR, detection rate; FIT, fecal immunochemical test; NA, not available; PPV, positive predictive value.

374 ^aAdvanced neoplasia indicates advanced adenoma and colorectal cancer.

^bAlso referred to as the adenoma detection rate. 375

^cDuring the first screening round, data for stage IV colorectal cancer in the total screening population were not collected. 376

378 Multivariate Poisson regression models were built to 379 estimate the rate ratio, with 95% CIs, for the association 380 between the screening round and each of the earlier-381 described performance measures. The second round 382 was used as a reference category.

383 Further analyses were restricted to the DR of CRC. 384 Multinomial logistic models were built to estimate the 385 probability of detection of CRC by disease site and tumor 386 stage compared with no detection. The probability was 387 expressed as a relative risk ratio, with 95% CIs, using the second screening round as a reference category. Anal 388 389 cancer cases were excluded from the estimate of the 390 probability of detection of CRC by disease site and tumor 391 stage. All models were adjusted for age.

392 All analyses were performed using SAS Enterprise 393 Guide (version 5.1; SAS Institute, Inc, Cary, NC) and STATA (version 15.1, Stata Corporation, College 394 395 Station, TX).

396 This study received Institutional Review Board 397 approval from the Romagna Cancer Institute (protocol 398 ID, L1P2043).

Results

Total Screening Population

Table 1 shows the absolute numbers of all subjects who were invited to screening, who participated, who tested positive, and who were diagnosed with adenoma and CRC in 5 organizational screening rounds. The resulting performance measures are shown in Table 2.

Compliant Participants: Numbers and Rates

Tables 3 to 6 consider only compliant participants. Table 3 provides their absolute numbers as well as the numbers of subjects with positive FIT results and with screen-detected disease.

Table 4 shows the performance measures under study, namely, the participation rate, the proportion of positive FIT results, the colonoscopic assessment rate, the DR of (and the PPV for) adenoma, advanced adenoma, CRC, and advanced neoplasia, and the DR of CRC by disease site and tumor stage. Contrasting these data with those from the total screening population, the second and subsequent rounds among compliant participants of both sexes were characterized by a smaller proportion of positive FIT results and a generally lower DR of advanced adenoma. The PPVs for advanced adenoma and advanced neoplasia also were lower.

Compliant Participants: Trends Across Rounds

Table 5 shows the rate ratios for the association between the screening round and the main of the earlier- Q17 described measures. The expected decrease between

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Results of 5 Rounds of FIT Screening

Table 3. Compliant Participants: Number of Subjects Eligible to, Invited to, and Participating in Five Screening Rounds, Number of Subjects With Positive FIT Results, Undergoing Colonoscopic Assessment, With Successful Cecal Intubation, and Diagnosed With Colorectal Adenoma and Colorectal Cancer, by Sex and Screening Round Males Females 2nd 3rd 4th 5th 2nd 3rd 4th 5th 1st 1st 215,681 254,292 88,491 Eligible 501,826 129,396 97,675 72,054 535,706 154,635 118,134 Invited 474,319 176,420 60,260 508,912 208,163 133,226 100,116 74,713 110,717 82.133 135,508 57,041 Participants 229,742 101,506 76,941 264,445 159,644 121,662 93,454 70,437 With positive FIT results 16,434 12,244 14,061 With colonoscopic assessment 10,153 With successful cecal intubation NA With adenoma Advanced adenoma Total adenoma With colorectal cancer Proximal colon Distal colon Rectum Anus^a Site unknown Stage I Stage II Stage III Stage IV Λ Stage unknown Total colorectal cancer

NOTE. All data are from the Emilia-Romagna Region colorectal cancer screening program (2005-2016). A compliant participant was defined as one who had 2, 3, 4, or 5 consecutive FITs at standard intervals (ie, 2 y ± 6 mo). A total of 1848 males and 2143 females with negative FIT results in the fourth screening round were considered not eligible for the fifth round because the length of follow-up time available in the case of positive FIT results was insufficient. The discrepancy between the number eligible and the number invited in each round is accounted for by subjects who died or migrated before invitation, subjects who were invited

or re-invited at age 70 or older, and subjects who were re-invited more than 2.5 years after the previous negative FIT.

FIT. fecal immunochemical test: NA. not available.

With advanced neoplasia^b

^aAnal cancer cases were excluded from the number of cases by tumor stage.

^bAdvanced neoplasia indicates advanced adenoma and colorectal cancer.

the first and the second round was confirmed for all of these, with the exception of the colonoscopic assessment rate. Between the second and the third round, a further 20% to 30% decrease was observed for males in the proportion of positive FIT results and in all DRs. PPVs decreased by 10% or less. Among females, these mea-sures decreased to a lesser extent.

At the fourth and fifth round, the DRs and the PPV for adenoma stabilized. Conversely, a further, albeit limited, decrease was observed for both sexes in the PPV for advanced adenoma, colorectal cancer, and advanced neoplasia. The tests for interaction between sex and screening round confirmed that the downward trend in most measures was more pronounced for males.

In Table 6, the relative risk ratios for the association between the screening round and the DR of CRC by disease site and tumor stage are shown. For both sexes, the DR of proximal colon cancer did not change further after the second round, whereas the yield of distal dis-ease continued to decrease until the fourth (males) and fifth (females) rounds. This observation should be related to the fact that the DR of proximal colon cancer, after plateauing, remained at a higher absolute level than that of distal colon cancer, especially among females

(Table 4). Regarding tumor stage, the DR of stage I and stage II CRC stabilized, for both sexes, only at the fourth round.

Discussion

Compared with the total screening population, compliant participants in the second and subsequent screening rounds had a lower proportion of positive FIT results and generally lower values for the DR of advanced adenoma and the PPV for advanced adenoma and advanced neoplasia. Data for organizational screening rounds refer to total participants, including subjects at their first FIT and subjects with occasional participation who had a screening interval longer than the standard. The prevalence of preclinical disease was higher in never-screened subjects and, albeit lower, increased with increasing screening intervals among ever-screened subjects. Thus, the earlier-described find-ings were expected.

With respect to compliant participants, the length of follow-up evaluation and the epidemiologic background of this study are comparable with the 2 complementary

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Table 4. Compliant Participants: Participation Rate, Proportion of Positive FIT Results, Colonoscopic Assessment Rate, Successful Cecal Intubation Rate, DR of Colorectal Adenoma and Colorectal Cancer, and PPV for Colorectal Adenoma and Colorectal Cancer, by Sex and Screening Round

	Round							
	1st	2nd	3rd	4th	5th			
Males								
Participation rate, %	48.4	76.8	91.7	93.7	94.7			
Proportion of positive FIT results, %	7.2	5.2	4.3	4.4	4.7			
Colonoscopic assessment rate, %	85.6	87.0	88.3	90.0	87.6			
Successful cecal intubation rate, %	NA	NA	NA	NA	NA			
DR of advanced adenoma (per 1000)	24.9	13.4	10.2	11.0	10.4			
DR of colorectal cancer (per 1000)	4.6	1.7	1.4	1.4	1.5			
DR of advanced neoplasia ^a (per 1000)	29.5	15.1	11.6	12.4	11.9			
PPV for adenoma, ^b %	56.3	49.4	46.4	47.7	45.8			
PPV for advanced adenoma, %	40.7	29.8	27.0	27.9	25.2			
PPV for colorectal cancer, %	7.5	3.8	3.8	3.5	3.6			
PPV for advanced neoplasia, ^a %	48.2	33.6	30.7	31.4	28.7			
DR of proximal colon cancer (per 1000)	1.0	0.5	0.6	0.5	0.6			
DR of distal colon cancer (per 1000)	2.6	0.7	0.5	0.3	0.4			
DR of rectal cancer (per 1000)	1.0	0.5	0.4	0.5	0.4			
DR of stage I colorectal cancer (per 1000)	2.5	0.8	0.8	0.7	0.7			
DR of stage II colorectal cancer (per 1000)	0.9	0.3	0.3	0.2	0.3			
DR of stage III colorectal cancer (per 1000)	0.8	0.3	0.2	0.3	0.2			
DR of stage IV colorectal cancer (per 1000)	0.2	0.1	<0.1	<0.1	0.1			
Females								
Participation rate, %	52.0	76.7	91.3	93.3	94.3			
Proportion of positive FIT results, %	4.6	3.7	3.3	3.4	3.8			
Colonoscopic assessment rate, %	82.9	84.8	87.8	88.2	86.8			
Successful cecal intubation rate, %	NA	NA	NA	NA	NA			
DR of advanced adenoma (per 1000)	11.7	6.4	5.4	5.5	5.7			
DR of colorectal cancer (per 1000)	2.4	1.1	1.1	0.8	1.0			
DR of advanced neoplasia ^a (per 1000)	14.1	7.5	6.5	6.3	6.7			
PPV for adenoma, ^b %	42.8	34.6	33.3	33.4	32.9			
PPV for advanced adenoma, %	30.5	20.4	18.5	18.0	17.2			
PPV for colorectal cancer, %	6.2	3.4	3.8	2.7	3.1			
PPV for advanced neoplasia, ^a %	36.7	23.8	22.3	20.8	20.3			
DR of proximal colon cancer (per 1000)	0.6	0.4	0.6	0.4	0.6			
DR of distal colon cancer (per 1000)	1.4	0.3	0.3	0.3	0.2			
DR of rectal cancer (per 1000)	0.4	0.3	0.2	0.2	0.2			
DR of stage I colorectal cancer (per 1000)	1.3	0.5	0.4	0.4	0.5			
DR of stage II colorectal cancer (per 1000)	0.4	0.2	0.2	0.2	0.1			
DR of stage III colorectal cancer (per 1000)	0.5	0.3	0.3	0.2	0.2			
DR of stage IV colorectal cancer (per 1000)	<0.1	<0.1	<0.1	0	<0.1			

620 NOTE. All data are from the Emilia-Romagna Region colorectal cancer screening program (2005-2016). A compliant participant was defined as one who had 2, 3, 621 4, or 5 consecutive FITs at standard intervals (ie, 2 y ± 6 mo). The participation rate is per 100 subjects invited. The proportion of positive FIT results is per 100 622 subjects undergoing FIT screening. The colonoscopic assessment rate is per 100 subjects with positive FIT results. The successful cecal intubation rate, if 623 available, would be per 100 subjects with positive FIT results undergoing colonoscopic assessment. The DRs of advanced adenoma, colorectal cancer, and advanced neoplasia are per 1000 subjects undergoing FIT screening. The PPVs are per 100 subjects with positive FIT results undergoing colonoscopic 624 assessment. Anal cancer cases were excluded from the number of cases by tumor stage.

625 DR, detection rate; FIT, fecal immunochemical test; NA, not available; PPV, positive predictive value.

626 ^aAdvanced neoplasia indicates advanced adenoma and colorectal cancer.

^bAlso referred to as the adenoma detection rate. 627

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studies by Zorzi et al,^{6,7} although they pooled males and 629 630 females in their study. In their data, the proportion of 631 positive FIT results, the DR of advanced adenoma, and 632 the PPV for advanced neoplasia decreased between the first and the second rounds and then stabilized, whereas 633 the DR of CRC decreased until the third round before 634 plateauing.⁶ Our results followed a similar pattern, but 635 all DRs as well as the proportion of positive FIT results 636 continued to decrease until the third round. In addition, 637 638 this trend was more pronounced for males.

Regarding the trends in the DR by disease site, our 687 findings were practically identical to those reported by 688 Zorzi et al⁷ for both sexes combined. The detection of 689 proximal colon cancer decreased between the first and 690 the second rounds and then stabilized, whereas the 691 detection of distal colon cancer decreased over 5 rounds. 692 In addition, the DR of proximal colon cancer remained at 693 a higher level than that of distal colon cancer, especially 694 among females. Many colonoscopy-verified diagnostic 695 studies¹² and studies on the proportional incidence of 696

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Table 5. Compliant Participants: Comparison of the First, Third, Fourth, and Fifth Screening Rounds Vs the Second Round for the Proportion of Positive FIT Results, the Colonoscopic Assessment Rate, the DR of Colorectal Adenoma and Colorectal Cancer, and the PPV for Colorectal Adenoma and Colorectal Cancer, by Sex

			Round			
	1st	2nd	3rd	4th	5th	P value
Males						
Proportion of positive FIT results	1.43 (1.39–1.47)	1.00 (ref)	0.79 (0.76–0.82)	0.78 (0.75–0.82)	0.81 (0.78–0.85)	
Colonoscopic assessment rate	0.98 (0.95–1.01)	1.00 (ref)	1.01 (0.97–1.06)	1.03 (0.99-1.08)	1.01 (0.96–1.06)	
DR of advanced adenoma	1.94 (1.84–2.05)	1.00 (ref)	0.72 (0.67–0.78)	0.75 (0.69-0.82)	0.68 (0.62-0.75)	
DR of colorectal cancer	2.85 (2.47-3.28)	1.00 (ref)	0.78 (0.63-0.96)	0.70 (0.55-0.88)	0.71 (0.55–0.91)	
DR of advanced neoplasia ^a	2.04 (1.94–2.15)	1.00 (ref)	0.73 (0.68–0.78)	0.74 (0.69-0.80)	0.68 (0.62–0.74)	
PPV for adenoma ^b	1.15 (1.10–1.19)	1.00 (ref)	0.93 (0.88–0.99)	0.95 (0.89-1.01)	0.91 (0.85–0.97)	
PPV for advanced adenoma	1.38 (1.31–1.45)	1.00 (ref)	0.90 (0.83–0.97)	0.93 (0.85-1.00)	0.83 (0.76–0.91)	
PPV for colorectal cancer	2.01 (1.74–2.31)	1.00 (ref)	0.96 (0.78–1.19)	0.86 (0.68-1.08)	0.86 (0.67–1.11)	
PPV for advanced neoplasia ^a	1.45 (1.38–1.52)	1.00 (ref)	0.91 (0.84–0.97)	0.92 (0.85-0.99)	0.83 (0.76–0.91)	
Females						
Proportion of positive FIT results	1.29 (1.25–1.33)	1.00 (ref)	0.86 (0.83–0.90)	0.86 (0.83-0.90)	0.93 (0.89–0.98)	<.0001
Colonoscopic assessment rate	0.98 (0.95–1.01)	1.00 (ref)	1.03 (0.99–1.08)	1.04 (0.99–1.09)	1.02 (0.97–1.08)	.8776
DR of advanced adenoma	1.89 (1.76–2.03)	1.00 (ref)	0.80 (0.72–0.88)	0.78 (0.70–0.87)	0.79 (0.70–0.89)	.0771
DR of colorectal cancer	2.36 (1.99–2.80)	1.00 (ref)	0.97 (0.77–1.21)	0.68 (0.52–0.89)	0.79 (0.60–1.04)	.0118
DR of advanced neoplasia	1.96 (1.84–2.09)	1.00 (ref)	0.82 (0.75–0.90)	0.77 (0.69–0.85)	0.79 (0.71–0.88)	.0050
PPV for adenoma ^o	1.25 (1.18–1.31)	1.00 (ref)	0.96 (0.89–1.03)	0.95 (0.88–1.03)	0.94 (0.86–1.02)	.0747
PPV for advanced adenoma	1.50 (1.40–1.61)	1.00 (ref)	0.90 (0.81–0.99)	0.87 (0.79–0.97)	0.83 (0.74–0.93)	.0374
PPV for colorectal cancer	1.86 (1.57–2.21)	1.00 (ref)	1.08 (0.86–1.36)	0.76 (0.58–0.99)	0.83 (0.63–1.09)	.5750
PPV for advanced neoplasia ^a	1.55 (1.45–1.66)	1.00 (ref)	0.92 (0.84–1.01)	0.86 (0.77–0.94)	0.83 (0.75–0.92)	.0742

NOTE. All data are from the Emilia-Romagna Region colorectal cancer screening program (2005–2016). A compliant participant was defined as one who had 2, 3, 4, or 5 consecutive FITs at standard intervals (ie, 2 y ± 6 mo). Numbers are rate ratios from multivariate Poisson regression models. Numbers in parentheses are 95% Cls.

DR, detection rate; FIT, fecal immunochemical test; PPV, positive predictive value.

^aAdvanced neoplasia indicates advanced adenoma and colorectal cancer. 725

^bAlso referred to as the adenoma detection rate. 726

^cTest for interaction between sex and screening round. 727

interval CRC^{13,14} showed a modest difference in the 729 730 sensitivity of FIT for proximal vs distal lesions.¹³ Other 731 investigations, however, have shown a substantially 732 lower sensitivity of FIT for right-sided tumors.^{7,15,16}

733 Previous studies have not evaluated trends in the 734 tumor-stage-specific probability of diagnosis of CRC af-735 ter the first round. We observed a decrease that was 736 distributed evenly among stage I and stage II CRC. The 737 DR of stage I and stage II CRC stabilized, for both sexes, 738 only at the fourth round.

Overall, the pattern of decrease in all DRs and, in 739 particular, the continuous decrease in the detection of 740 741 distal colon cancer for 5 rounds confirmed the notion 742 that the diagnoses of advanced adenoma were cumulative over the screening rounds.⁷ These data also pro-743 018 744 vided circumstantial evidence that FIT screening prevents the progression of an appreciable subset of 745 advanced adenomas.^{3,6,7} Indeed, because the sensitivity 746 of FIT can be assumed to be constant across rounds, the 747 748 changes in the DRs of CRC and distal colon cancer can be 749 explained only with a decrease in the prevalence of 750 preclinical detectable CRC and distal colon cancer. This, 751 in turn, only can be the result of the detection and 752 treatment of some advanced adenomas next to become 753 <mark>Q19</mark> invasive diseases. Whether this may translate into a 754 significant reduction in the absolute incidence of CRC

compared with a nonscreening situation is a question that warrants further research. 17,18

Our results have policy implications. First, organized or programmatic cancer screening models have advantages over opportunistic screening practice including, for example, larger coverage and lower risk of overdiagnosis and overtreatment. Our findings indicate that a regular invitation-re-invitation system also would increase the cumulative sensitivity of FIT screening and its effectiveness in preventing distal CRC.

Second, people with compliant participation in 5 screening rounds, necessarily coupled with negative FIT results, should be informed that they have a substantial decrease in the risk of being diagnosed with an advanced lesion. Screening programs aim to maximize their effectiveness by maximizing the uptake. Over the years, however, the imperative to ensure that people invited make an informed choice about participating or not has emerged and now is widely accepted.

Third, our results may be of help in the planning of 806 endoscopy services. Different approaches are being 807 developed to prioritize the access of patients, to create 808 appropriate time slots for them, and to allocate the most 809 experienced endoscopists based on the expected diag-810 nostic yield. The criteria currently used include the 811 indication¹⁹ and other clinical characteristics of 812

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Table 6. Compliant Participants: Comparison of the First, Third, Fourth, and Fifth Screening Rounds Vs the Second Round for the DR of Colorectal Cancer by Disease Site, Tumor Stage, and Sex

	Round							
	1st	2nd	3rd	4th	5th			
Males								
DR of proximal colon cancer	2.01 (1.54–2.63)	1.00 (ref)	1.03 (0.73–1.46)	0.91 (0.62–1.34)	1.00 (0.67-1.50)			
DR of distal colon cancer	3.80 (3.07-4.70)	1.00 (ref)	0.60 (0.42-0.84)	0.37 (0.24-0.58)	0.43 (0.27-0.69			
DR of rectal cancer	2.32 (1.75-3.07)	1.00 (ref)	0.79 (0.53-1.18)	0.96 (0.64-1.44)	0.74 (0.46-1.20			
DR of stage I colorectal cancer	3.15 (2.57-3.85)	1.00 (ref)	0.86 (0.64-1.15)	0.73 (0.53-1.02)	0.72 (0.51-1.03			
DR of stage II colorectal cancer	2.66 (1.93-3.65)	1.00 (ref)	0.92 (0.59–1.43)	0.54 (0.31-0.94)	0.68 (0.39-1.18			
DR of stage III colorectal cancer	2.51 (1.81–3.46)	1.00 (ref)	0.57 (0.34–0.96)	0.74 (0.44–1.23)	0.55 (0.30-1.02)			
DR of stage IV colorectal cancer	3.73 (1.68-8.29)	1.00 (ref)	0.36 (0.07–1.74)	0.45 (0.09–2.19)	0.88 (0.22-3.45			
Females								
DR of proximal colon cancer	1.39 (1.05–1.85)	1.00 (ref)	1.16 (0.83–1.61)	0.76 (0.51–1.13)	1.11 (0.76–1.62			
DR of distal colon cancer	4.37 (3.27–5.84)	1.00 (ref)	0.93 (0.62-1.40)	0.68 (0.42-1.10)	0.46 (0.25–0.85			
DR of rectal cancer	1.57 (1.10–2.24)	1.00 (ref)	0.74 (0.46-1.20)	0.56 (0.32-0.99)	0.66 (0.37-1.18			
DR of stage I colorectal cancer	2.81 (2.20-3.59)	1.00 (ref)	0.84 (0.59-1.18)	0.71 (0.48–1.05)	0.83 (0.56–1.23			
DR of stage II colorectal cancer	2.53 (1.66–3.86)	1.00 (ref)	1.17 (0.68-2.01)	0.88 (0.47–1.63)	0.68 (0.33-1.42)			
DR of stage III colorectal cancer	1.54 (1.12–2.12)	1.00 (ref)	0.88 (0.58-1.32)	0.58 (0.35–0.96)	0.60 (0.35–1.03			
DR of stage IV colorectal cancer	4.15 (0.86–19.99)	1.00 (ref)	3.70 (0.80–17.12)	0	0.90 (0.09–9.36)			

NOTE. All data are from the Emilia-Romagna Region colorectal cancer screening program (2005-2016). A compliant participant was defined as one who had 2, 3, 4, or 5 consecutive FITs at standard intervals (ie, 2 y ± 6 mo). Numbers are as relative risk ratios from multinomial logistic regression models. Numbers in parentheses are 95% Cls. Anal cancer cases were excluded from the number of cases by tumor stage.

836 DR. detection rate.

> patients.²⁰ Our results suggest that compliant long-term participation in FIT screening must be included among the latter.

Fourth, these findings have relevance to the hypoth-842 843 esis of using risk prediction models based on established 844 risk factors for allocation to personalized screening in-845 tervals and/or protocols. A systematic review showed 846 that screening history is not among the most commonly 847 used risk factors (age, sex, family history, obesity, and smoking).²¹ For subjects allocated to standard FIT 848 screening, however, a compliant participation in 5 to 6 849 rounds may alter the risk of disease to a substantial 850 extent. We agree with the view that screening history 851 cannot be ignored.²² The number of previous negative 852 853 tests, if combined with the amount of hemoglobin in 854 negative FIT, could identify a small group with very high risk and a large population with minimal risk.²³ For 855 example, Zorzi et al⁶ proposed increasing the cut-off 856 857 value for positivity or extending the screening interval 858 for women and younger individuals after 3 negative FITs 859 (provided that the incidence of interval cancer does not 860 exceed the maximum acceptable levels).

861 This study had some major weaknesses. First, the 862 sharp decrease in the number of subjects undergoing FIT 863 between the first and the fifth round-inherent to the study design-caused an increasing random variation in 864 results. The decrease in the number of compliant par-865 866 ticipants, however, mainly was owing to external factors 867 (ie, late invitation, screening cessation at age 70 years, 868 migration, and death). These factors accounted, for example, for more than 75% of subjects who participated 869 in the fourth round, but not in the fifth round (data not 870

shown). This suggests that the findings of the last rounds were not affected by major selection biases.

Second, previous studies have shown that the performance measures of follow-up rounds depend on the number of FITs and the chosen cut-off values. With lower cut-off values or with 2 FIT screenings, more advanced neoplasias were detected at the baseline round, and fewer during subsequent rounds.⁸ Consequently, our results cannot be generalized to different screening protocols.

Theoretically, studies of this type may be affected by 907 908 another potential bias that relates to those subjects with positive FIT results and negative colonoscopy who are 909 re-invited to screening some rounds later. These sub-910 911 jects, who are at low risk of disease, might influence the 912 results at subsequent rounds. It must be noted, however, that this cannot be the case for the present study, in 913 which follow-up evaluation ceased on the day of receipt 914 of colonoscopy for a positive FIT result. 915

In summary, compliant participants had a lower Q20 916 proportion of positive FIT results than the total 917 screening population. For them, some major perfor-918 919 mance measures continued to decrease even after the expected decrease between the first and the second 920 rounds. Between the second and the third rounds, the 921 proportion of positive FIT results and the DR of 922 advanced adenoma, CRC, and advanced neoplasia 923 decreased by 20% to 30% among males. For both sexes, 924 the DR of distal colon cancer decreased until the fourth 925 926 (males) and fifth rounds (females). These findings add circumstantial evidence that FIT screening prevents the 927 progression of an appreciable subset of advanced 928

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adenomas, and have implications for the communication of benefits and harms of the screening process, the planning of endoscopy services, and the development of risk-based screening strategies.

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