ISTITUTO PER LO STUDIO
E LA PREVENZIONE ONCOLOGICA

DELIBERAZIONE DEL DIRETTORE GENERALE

(Nominato con D.P.G.R.T. n. 201 del 19/12/2013)

N° 153 del 30/06/2016

Oggetto: Recepimento della convenzione tra la Regione Toscana e ISPO per la realizzazione del progetto *"The value of HPV DNA testing using self-collected sampling in non-attendees cervical cancer screening end molecular triage strategies on self-sampled material for HPV positive women".*		
Struttura Proponente	S.C. Amministrazione, Gestione risorse, Attività tecniche e Supporto alla ricerca	
	S.S. Bilancio, Contabilità e Investimenti	
Proposta n.	Responsabile del procedimento	Manola Turci
	Estensore	Manola Turci

IMMEDIATAMENTE ESEGUIBILE [x]

Conto Economico n.

Eseguibile a norma di Legge dal 30/06/2016

Pubblicato a norma di Legge il 30/06/2016

Inviato al Collegio Sindacale il 30/06/2016

IL DIRETTORE GENERALE

di questo Istituto per lo Studio e la Prevenzione Oncologica , con sede in Via Cosimo Il Vecchio 2 – 50139 Firenze, in forza del Decreto del Presidente della Giunta Regionale Toscana n. 201 del 19/12/2013.

Visto il D. Lgs. vo 30/12/1992 n. 502 e sue successive modifiche ed integrazioni e la L. R. Toscana n. 40 del 24/02/2005 di disciplina del Servizio Sanitario Regionale e successive modificazioni ed integrazioni;

Vista la Legge Regionale Toscana n. 3 del 04/02/2008, modificata con Legge Regionale n. 32 del 19.06.2012, in forza della quale ISPO (Istituto per lo Studio e la Prevenzione Oncologica) è ente del Servizio Sanitario Regionale dotato di personalità giuridica pubblica e di autonomia organizzativa, amministrativa e contabile;

Vista la delibera del Direttore Generale n. 4 del 12.01.2012 con la quale è stato approvato il regolamento dei progetti finalizzati;

Preso atto che con Decreto Dirigenziale n. 5224 del 04.12.2013 avente per oggetto "*ITT – Approvazione del Bando per l'assegnazione di fondi per il finanziamento di progetti per la ricerca in campo oncologico – anno 2013 – e della relativa modulistica*" è stato approvato e indetto un avviso pubblico per il finanziamento di progetti di ricerca annuali, biennali e triennali in campo oncologico;

Dato atto che in attuazione di suddetto bando con Decreto Dirigenziale n. 6685 del 15.12.2014, a seguito dell'iter valutativo previsto, sono stati approvati dall'Ufficio di Direzione dell'ITT 26 progetti di ricerca tra cui il progetto dal titolo "*The value of HPV DNA testing using self-collected sampling in non-attendees cervical cancer screening end molecular triage strategies on self-sampled material for HPV positive women*", presentato per ISPO dalla Dott.ssa Francesca Carozzi, Dirigente Biologo presso la S.C. Laboratorio Regionale di Prevenzione Oncologica;

Visto che con Decreto Dirigenziale n. 623 del 23.02.2015 la Regione Toscana ha approvato lo schema di convenzione per disciplinare i rapporti tra la Regione Toscana e gli enti assegnatari dei finanziamenti;

Visto il testo di convenzione tra ISPO e la Regione Toscana, allegato alla presente sotto lettera "A" quale parte integrante e sostanziale, nel quale si stabiliscono le modalità di realizzazione delle attività da parte di ISPO;

Preso atto che tra le modalità di realizzazione delle attività è prevista la partecipazione, per il primo anno di attività, di due Additional Unit che dovranno arruolare le donne in base ai criteri del protocollo di studio;

Precisato che con successivo atto sarà approvata apposita convenzione che regoli le attività progettuali tra ISPO e le Additional Unit ex Azienda USL 12 Viareggio, ora USL Toscana Nord Ovest e la ex Azienda USL 1 Massa, ora USL Toscana Nord;

Rilevato, che il progetto su citato prevede l'arruolamento di donne non rispondenti al precedente round di screening e che per tale motivo si è reso necessario, come previsto tra l'altro nell'art. 10 della convenzione con la Regione Toscana, richiedere il parere al Comitato Etico Area Vasta Centro per ISPO e del Comitato Etico di Area Vasta Nord Ovest per le Additional Unit ;

Vista la nota prot. SPE 15.093 del 14.12.2015, agli atti, con la quale il Comitato Etico di Area Vasta Centro, ha espresso parere favorevole allo svolgimento dello studio clinico;

Vista la nota prot. 36743 del 16/06/2016, agli atti, con la quale il Comitato Etico di Area Vasta Nord Ovest , ha espresso parere favorevole allo svolgimento dello studio clinico;

Ritenuto di dichiarare il presente atto immediatamente eseguibile per consentire in tempi brevi l'avvio del progetto e l'arruolamento delle donne non rispondenti al precedente round di screening;

Vista la Delibera n. 292 del 24/12/2015 di "Approvazione del nuovo Regolamento di Organizzazione e Funzionamento dell'Istituto per lo Studio e la Prevenzione Oncologica";

Con la sottoscrizione del Direttore Amministrativo e del Direttore Sanitario, ciascuno per quanto di competenza (ai sensi del D. Lgs. 502/92 e ss.mm. e ii.)

DELIBERA

Per quanto esposto in narrativa:

1. di approvare lo schema di convenzione con la Regione Toscana per il progetto "*The value of HPV DNA testing using self-collected sampling in non-attendees cervical cancer screening end molecular triage strategies on self-sampled material for HPV positive women*" allegato alla presente sotto lettera "A" quale parte integrale e sostanziale;

2. di stabilire che con successivo atto sarà approvata apposita convenzione che regoli le attività progettuali tra ISPO e le Additional Unit ex Azienda USL 12 Viareggio, ora USL Toscana Nord Ovest e la ex Azienda USL 1 Massa, ora USL Toscana Nord;

3. di prendere atto del parere favorevole espresso dal Comitato Etico Area Vasta Centro per ISPO e del Comitato Etico di Area Vasta Nord Ovest per le Additional Unit;

4. di dichiarare il presente atto immediatamente eseguibile ai sensi della normativa vigente;

5. di trasmettere il presente atto all'albo di pubblicità degli atti di questo Istituto e al Collegio Sindacale.

IL DIRETTORE SANITARIO
Dr. Riccardo Poli

IL DIRETTORE AMMINISTRATIVO
Dr. Fabrizio Carraro

IL DIRETTORE GENERALE
Prof. Gianni Amunni

Elenco degli allegati

Strutture aziendali da partecipare:

S.C. Laboratorio Regionale di Prevenzione Oncologica ISPO;
S.S. Laboratorio Regionale HPV e Biologia Molecolare;
S.S. Bilancio, Contabilità e Investimenti ISPO;
Settore Attività Amministrative di Supporto Area Ricerca ISPO;
Dipartimento Amministrazione e Finanza ASF.

Allegato "1"

REGIONE TOSCANA

Giunta Regionale

Progetti di ricerca ITT

CONVENZIONE

tra la Regione Toscana e l'Istituto per lo Studio e la Prevenzione Oncologica per la realizzazione del progetto: *"The value of HPV DNA testing using self-collected sampling in non-attendees cervical cancer screening and molecular triage strategies on self-sampled material for HPV positive women".*

La **RegioneToscana**, (di seguito chiamata Regione), Codice Fiscale 01386030488, in persona dell' Avv. Katia Belvedere, dirigente del settore Consulenza Giuridica, Ricerca e supporto Organismi di Governo Clinico ai sensi del Decreto n. 4303 del 29/09/2015 ed autorizzata, ai sensi della L.R. 1/2009, a sottoscrivere la presente convenzione approvata in schema con decreto n. 623 del 23/02/2015;

E

l'Istituto per lo Studio e la Prevenzione Oncologica, (di seguito chiamato ISPO) Codice Fiscale 94158910482 in persona del Prof. Gianni Amunni, Direttore Generale dell'ISPO, nato a San Giovanni Valdarno (AR) il 06/08/1954;

PREMESSO

- che la Regione con Decreto Dirigenziale n. 5254 del 04.12.2013 avente per oggetto "TTT - Approvazione del Bando per l'assegnazione di fondi per il finanziamento di progetti per la ricerca in campo oncologico - anno 2013 – e della relativa modulistica" ha approvato e di seguito diffuso un avviso pubblico;

- che la Regione in attuazione del suddetto Bando, con Decreto Dirigenziale n. 6685 del ha approvato il progetto, denominato *"The value of HPV DNA testing using self-collected sampling in non-attendees cervical cancer screening and molecular triage strategies on self-sampled material for HPV positive women";*

- che l'ISPO è in possesso dei titoli e dei requisiti richiesti dal Bando in oggetto per

svolgere correttamente il progetto di ricerca;

- che il responsabile del progetto di ricerca è la Dr.ssa Francesca Maria Carozzi, nata a Carrara l'11/09/1956;

- che il responsabile del progetto di ricerca condivide il contenuto della presente convenzione;

- che il codice CUP è: F12I14000310002.

TUTTO CIÒ PREMESSO SI CONVIENE E SI STIPULA QUANTO SEGUE:

Art. 1

Premessa

La premessa costituisce parte integrante ed essenziale della presente convenzione.

Art. 2

Soggetto attuatore

L'ISPO, successivamente indicato anche come "soggetto attuatore", si impegna verso la Regione, a curare l'organizzazione e l'effettuazione delle attività indicate nel progetto di ricerca come sopra denominato, successivamente indicato semplicemente progetto, di cui si allega copia sotto la lettera A), quale parte integrante ed essenziale della presente convenzione.

Il soggetto attuatore, per la realizzazione delle attività progettuali, dovrà avvalersi di personale in possesso delle necessarie caratteristiche professionali specifiche; e si impegna al pieno rispetto della normativa in vigore, in particolare quella relativa alla sicurezza sui luoghi di lavoro. La Regione resta comunque estranea a qualsiasi rapporto di lavoro e collaborazione a qualunque titolo instaurato dal soggetto attuatore nello svolgimento e per le necessità del programma.

Art. 3

Finanziamento del progetto

Il progetto è finanziato dalla Regione per un costo complessivo di €. 144.000 (centoquarantaquattromila/00), secondo le modalità di erogazione previste al successivo art. 5, così ripartite, 1° anno €. 85.000, 2° anno €. 59.000.

Il soggetto attuatore dichiara altresì che non esistono co-finanziamenti.

In particolare il soggetto attuatore dichiara di non cumulare il finanziamento approvato con altri ulteriori finanziamenti pubblici o privati già ottenuti per realizzare le stesse azioni e che non verranno chiesti in futuro altri finanziamenti pubblici per la realizzazione delle stesse azioni.

Il finanziamento previsto a carico della Regione si deve intendere al lordo di qualsiasi

spesa e costituisce il tetto massimo di spesa rimborsabile. L'erogazione del saldo, al termine del progetto di ricerca, sarà subordinato all'obbligo di documentare le spese effettivamente sostenute, come meglio precisato anche nei successivi articoli della presente convenzione. La mancata presentazione, senza giustificato motivo della documentazione suddetta, entro i termini previsti dai successivi articoli, comporterà la decadenza del diritto al rimborso, nonché il recupero degli acconti già erogati, fatte salve eventuali altre azioni per la tutela degli interessi della Pubblica Amministrazione nelle sedi opportune.

Poiché trattasi di un contributo di ricerca, il finanziamento è fuori campo di applicazione IVA e non è oggetto alla ritenuta di acconto del 4% ai sensi dell'art. 28 del DPR 600/73.

Art. 4

Comunicazione di avvio del progetto

Entro **45 (quarantacinque) giorni** dalla firma della presente convenzione, dovrà pervenire alla **Regione - Settore Consulenza Giuridica, Ricerca e supporto Organismi di Governo Clinico** - una lettera firmata dal Responsabile del progetto, contenente l'indicazione puntuale della data di avvio del progetto che non può essere successiva alla lettera di comunicazione nè antecedente alla data del decreto di approvazione dei progetti. Il mancato ricevimento della comunicazione entro i 45 (quarantacinque) giorni comporterà la risoluzione della convenzione e non potrà essere rimborsata nessun tipo di spesa.

Art. 5

Erogazione del Finanziamento

La Regione, in conformità del Bando Regionale in oggetto, si impegna ad erogare le somme di cui al precedente art. 3, al ricevimento della documentazione richiesta e con le seguenti modalità:

Il finanziamento relativo ai **progetti biennali** verrà erogato, salvo eccezioni, come segue:

a) la prima erogazione, pari al 100% dell'importo finanziato per il primo anno, dopo la lettera che comunica la data di avvio del progetto di ricerca, come da art. 4

b) la seconda erogazione, pari al 70% dell'importo finanziato per il secondo anno, dietro presentazione, nei 30 giorni successivi alla scadenza del primo anno, dei seguenti documenti:

- Relazione scientifica sullo stato di avanzamento del progetto;
- Rendiconto delle spese effettivamente sostenute nell'intero primo anno di ricerca, da predisporre con gli stessi criteri utilizzati per la definizione del preventivo (vedi tab. 16 rimodulata, allegata sotto la lettera B) alla presente convenzione. Il rendiconto dovrà esse redatto in relazione alle spese effettivamente sostenute per ogni singola voce del progetto, sulla base dei costi ammissibili previsti dalla normativa vigente;

- Dichiarazione sostitutiva resa ai sensi del DPR 28 Dicembre 2000, n. 445, con la quale il responsabile del progetto di ricerca attesta la veridicità ed esattezza dei dati esposti e dei documenti prodotti.

Si intende quindi che il 30% del finanziamento del secondo anno sarà anticipato dal soggetto attuatore; l'erogazione del saldo avverrà al termine della verifica dei documenti, nella misura delle spese effettivamente sostenute e documentate nel biennio, come dal successivo articolo 7.

Eventuali spostamenti di somme tra voci di spesa o da un anno all'altro, dovranno essere preventivamente autorizzati dalla Regione Toscana.

L'esame della documentazione richiesta dovrà essere effettuato dagli organismi competenti entro 60 giorni dalla ricezione, in particolare la relazione scientifica sarà sottoposta a valutazione del Direttore Scientifico dell'ITT; entro tale termine dovrà essere inoltre data comunicazione al responsabile del progetto sull'esito della verifica effettuata.

L'ultima rata del finanziamento verrà erogata a saldo delle spese effettivamente sostenute nella durata dell'intero progetto, rispettando il tetto massimo di spesa rimborsabile.

Entro 60 giorni dal termine del progetto, dovranno essere inviati i seguenti documenti:

- Relazione scientifica conclusiva stilata dal responsabile del progetto, corredata di eventuali pubblicazioni che dovranno citare il supporto della Regione Toscana -ITT;
- Rendiconto economico finale complessivo secondo quanto indicato al successivo art. 7;
- Dichiarazione sostitutiva resa ai sensi del DPR 28 Dicembre 2000, n. 445.

La documentazione finale dovrà essere approvata dall'Ufficio di Direzione dell'ITT entro 60 giorni dal ricevimento.

Ritardi o mancanza nel sottoporre questa documentazione potranno avere effetti negativi su successive richieste di finanziamento.

La Regione attuerà delle verifiche a campione, istituendo apposita Commissione per i controlli, sui documenti giustificativi di spesa relative alle dichiarazioni sostitutive rese ai sensi del DPR 28 Dicembre 2000, n. 445. Il soggetto attuatore si impegna a restituire alla Regione gli importi da questa ricevuti, ma non riconosciuti ammissibili dall'Amministrazione stessa in sede di verifica finale del progetto, relativamente all'attività svolta. Il soggetto attuatore si impegna a restituire tali importi nelle forme e tempi indicati dalla Regione, fatto salvo il proprio diritto a prendere visione e controllare il verbale di accertamento finale delle spese, redatto in sede di verifica finale. L'eventuale recupero dei finanziamenti indebitamente ricevuti dal beneficiario finale sarà incrementato dagli interessi calcolati in base alla normativa vigente. La suddetta Commissione potrà effettuare i controlli entro e non oltre i 3 anni successivi al termine del

progetto.

Art. 6
Durata del Progetto - Proroga- Sospensione

Il progetto ha la durata di 2 anni.

Il progetto non potrà subire né modifiche né proroghe salvo in casi del tutto eccezionali. Il soggetto attuatore o il responsabile del progetto di ricerca invieranno motivata e ben documentata richiesta scritta alla Regione che, acquisito il parere del Direttore Scientifico dell'ITT, accorderà o meno tale richiesta. La concessione della eventuale proroga, che sarà subordinata alla riconosciuta sussistenza di ragioni di necessità e d'opportunità, non costituisce motivo di maggiorazione del corrispettivo accordato.

Qualora sia accertata la mancata o irregolare attuazione del programma la Regione potrà sospendere l'erogazione del finanziamento.

Il Responsabile del progetto può, in casi eccezionali e per giustificati motivi richiedere la sospensione del progetto. La sospensione può essere richiesta per un anno al massimo, eccezionalmente prorogabile ad un altro anno, nel caso sussistano i giustificati motivi.

Art. 7
Rendiconto finale

Il soggetto attuatore si impegna a presentare alla Regione, entro 60 (sessanta) giorni dal termine delle attività, il rendiconto finale relativo alle spese effettivamente sostenute nella durata dell'intero progetto. Tale rendiconto verrà presentato utilizzando la tabella 16 e specificando all'interno di ogni macrovoce le singole voci di spesa, anno per anno, sulla base dei costi ammissibili previsti dalla normativa vigente.

Questo dovrà essere corredato dalla relazione illustrativa delle attività svolte e da una dichiarazione sostitutiva resa ai sensi del DPR 28 Dicembre 2000, n. 445, con la quale il responsabile del progetto di ricerca attesti la veridicità ed esattezza dei dati esposti e dei documenti prodotti.

Per quanto concerne l'I.V.A. e le altre imposte dirette o indirette che possono essere recuperate, rimborsate o compensate in qualsiasi modo e che pertanto non restano definitivamente a carico del soggetto attuatore, beneficiario finale del finanziamento, non possono essere ammesse a rimborso.

I documenti giustificativi di tutte le spese sostenute nel corso dell'attuazione del progetto, dovranno essere conservati secondo le norme di legge ed esibiti in originale, su richiesta della Regione, per le verifiche previste dall'art. 5.

Art. 8
Trasmissione documenti

I documenti di cui agli artt. 4 - 5 - 6 - 7 ed ai successivi artt. 9 e 11 dovranno essere trasmessi alla Regione Toscana - Settore Consulenza Giuridica, Ricerca e supporto Organismi di Governo Clinico - all' indirizzo PEC: **regionetoscana@postacert.toscana.it** tramite casella PEC del soggetto attuatore. In caso di malfunzionamento della trasmissione telematica o impossibilità di utilizzarla, la trasmissione dei documenti di cui sopra potrà essere effettuata a mezzo posta raccomandata con ricevuta di ritorno indirizzata alla Regione Toscana - Settore Consulenza Giuridica, Ricerca e supporto Organismi di Governo Clinico.

Art. 9
Responsabile del progetto di ricerca

Se nel corso della durata del progetto termina il rapporto di lavoro tra il responsabile del progetto ed il soggetto attuatore, il finanziamento si intende sospeso. Se ne esistono i presupposti, il soggetto attuatore in accordo con il responsabile del progetto possono far richiesta alla Regione Toscana affinché il finanziamento venga corrisposto ad altro soggetto attuatore o ad altro responsabile.

Art. 10
Parere Comitato Etico Regionale

Se il progetto prevede la sperimentazione umana e l'utilizzo di campioni biologici umani, deve essere richiesto, prima dell'avvio del progetto, il parere al Comitato Etico Regionale per la sperimentazione clinica (sezione del comitato etico di riferimento) e deve essere inviata alla Regione copia dell' autorizzazione ricevuta dall'autorità competente ai sensi della normativa vigente. Se il progetto prevede la sperimentazione su animali o loro campioni biologici, deve essere inviata alla Regione, prima dell'avvio del progetto, la copia dell'autorizzazione rilasciata ai sensi del DLGS n. 26 del 04/03/2014.

Art. 11
Proprietà dei risultati e pubblicazione

Qualora il responsabile del progetto intenda procedere alla pubblicazione scientifica o divulgazione in forma orale e/o scritta di risultati, concernenti l'attività di ricerca relativa al progetto, potenzialmente suscettibili di tutela brevettuale, il responsabile del progetto dovrà farne richiesta attraverso comunicazione scritta alla Regione Toscana come da art. 8, allegando bozza della proposta di pubblicazione o della divulgazione. La richiesta si considera accolta qualora la Regione Toscana, entro 30 (trenta) giorni dal ricevimento della predetta richiesta da parte del responsabile del progetto, non comunichi il proprio diniego.

La Regione Toscana si avvarrà della collaborazione dell'Ufficio per la Valorizzazione della Ricerca Biomedica e Farmaceutica (UVaR), istituito presso la Direzione Generale Diritti di cittadinanza e coesione sociale, per la valutazione dei requisiti di brevettabilità dei

risultati oggetto della suddetta pubblicazione e per eventuali azioni, concordate fra le parti, a tutela e valorizzazione della proprietà intellettuale relativa ai risultati derivanti dal progetto.

In caso di pubblicazione anche parziale dei risultati, è obbligatorio citare che la ricerca è stata fatta con il contributo della Regione Toscana-ITT.

La proprietà dei risultati eventualmente brevettabili sarà definita in ottemperanza a quanto stabilito dal "Codice della Proprietà Industriale" emanato con D. Lgs. 10 febbraio 2005, n. 30 a norma dell'art. 15 della L. 12.12.2002, n. 273 salvo particolari accordi che potranno essere stipulati anche successivamente tra le parti firmatarie del presente atto.

I proprietari dei risultati concedono l'uso degli studi, dei prodotti e delle metodologie sopra descritti per le finalità che le sono proprie, ferma restando la loro disponibilità in favore del Servizio Sanitario Regionale.

Art. 12
Foro Competente

Per ogni controversia che dovesse insorgere con riferimento alla presente convenzione è competente il Foro di Firenze.

Art. 13
Trattamento dati personali

Il trattamento dei dati personali viene effettuato ai sensi dell'art. 18 comma 2 del Decreto Legislativo n. 196 del 30 giugno 2003, per l'esclusivo svolgimento delle funzioni istituzionali dell'ente.

Art.14
Oneri Fiscali

In caso d'uso la presente convenzione verrà registrata a tassa fissa, ai sensi del II comma dell'art. 5 (caso d'uso) e dell'art. 38 (tassa fissa) del DPR 26.10.72, n. 634 e successive modifiche ed integrazioni, a cura e spese del richiedente la registrazione.

E' inoltre esente da bollo, ai sensi dell'art. 16, tab. B del DPR 26.10.72, n. 642, come modificato dall'art. 28 del DPR 30.12.82, n. 955.

Letto, approvato e sottoscritto

Per Regione Toscana **Katia Belvedere**

Per ISPO **Gianni Amunni**

Allegato "A"

ISTITUTO TOSCANO TUMORI (ITT) – REGIONE TOSCANA
GRANT PROPOSAL 2013

1. PRINCIPAL INVESTIGATOR (PI)

FIRST AND LAST NAME	FRANCESCA MARIA CAROZZI
POSITION TITLE	BIOLOGIST
INSTITUTION	ISPO - CANCER PREVENTION AND RESEARCH INSTITUTE
ADDRESS	VIA COSIMO IL VECCHIO 2
CITY	FLORENCE
PHONE	055 32697852
E-MAIL	f.carozzi@ispo.toscana.it
LEGAL REPRESENTATIVE	PROF GIANNI AMUNNI
ADDRESS	ISPO- FLORENCE
E-MAIL	Direzione.generale@ispo.toscana.it

2. PROJECT TITLE (Max 150 Characters)

The value of HPV DNA testing using self-collected sampling in non-attendees cervical cancer screening and molecular triage strategies on self-sampled material for HPV positive women.

2.1 KEY-WORDS

HPV
Self sampling
DNA Methylation

3. ESTIMATED COMPREHENSIVE COSTS OF THE PROPOSED RESEARCH

Grant Requested to ITT (see n.16.5)	226.500 Euros
Available Grant(s) co-financing the Proposal (see n. 17/17.1)	None

4. PROJECT TIME-FRAME

Annual	
Biennal	
Triennal	X

5. EXTERNAL COLLABORATORS INVOLVED IN THE PROJECT (ADDITIONAL RESEARCH UNITS)

FIRST AND LAST NAME OF THE COLLABORATOR	INSTITUTION (FULL NAME AND ADDRESS)
Aurora Assunta Scarfantoni	Azienda USL 12 di Viareggio - Via Aurelia 335, Lido di Camaiore (LU)
Roberta Rosati	Azienda USL 9 di Grosseto - Via Cimabue, 109 - 58100 Grosseto -
Cristina Nicolai	Azienda USL 1 di Massa e Carrara - Via Don Minzoni, 3 - Carrara (MS)

6. SIGNATURES

Principal Investigator – Firma leggibile	Legal Representative – (o soggetto delegato alla firma) Firma leggibile e timbro
Francesca Maria Carozzi	Gianni Amunni PROF. GIANNI AMUNNI DIRETTORE GENERALE ISPO

6.1 DICHIARAZIONE DEL LEGALE RAPPRESENTANTE o DEL SOGGETTO DELEGATO ALLA FIRMA (obbligatoria)

Il Sottoscritto .....Gianni Amunni..... , in qualità di ..Direttore Generale ISPO .....

DICHIARA:

a) che il PI che presenta il progetto fa parte del personale "strutturato", dipendente con contratto a tempo indeterminato o determinato, dell'istituzione proponente;
b) che sul progetto presentato non esiste altra fonte di finanziamento se non quello dichiarato al punto 3. e specificato nel punto 17 e seguenti;
c) di approvare quanto dichiarato al punto 16 e seguenti ed in particolare la tabella "justification on budget"

Firma (leggibile) e Timbro del Legale Rappresentante (o Soggetto Delegato)

.....PROF. GIANNI AMUNNI..
DIRETTORE GENERALE ISPO

6.2 DICHIARAZIONE DEL SOGGETTO DELEGATO

Se il progetto non è firmato dal Legale Rappresentante è necessario sottoscrivere anche la seguente dichiarazione:

Il Sottoscritto..... DICHIARA ai sensi degli artt. 46 e 47 del DPR 445/2000 e consapevole delle responsabilità previste dagli artt. 75 e 76 del DPR 445/2000 per le ipotesi di falsità in atti e dichiarazioni mendaci, di essere legittimato a firmare essendo in possesso di delega del Legale Rappresentante.

Firma leggibile e Timbro .....

6.3 DICHIARAZIONE DEL P.I.

Il P.I. nell'inoltrare la domanda, DICHIARA specificatamente, che sarà presenta a tempo pieno nell'Ente in cui si svolge il progetto.

Firma leggibile del P.I....

7. ABSTRACT (Max 2800 Characters)

In most industrialised countries, the majority of invasive cervical cancers occur among women who have not attended cervical screening. In Tuscany the coverage of cervical cancer screening program is about 100% but the response to the invitation is 56% and more than 67% of invasive cancer occurs in never screened women or under-screened women.

As a consequence, the heaviest and most immediate impact on cervical cancer prevention can be obtained only by improving the test coverage.

An item that got much attention in the last couple of years involves the use of self-collected cervico-vaginal material. The opportunity of a home, self-collected sample, opens the chance to remove some of the barriers that may discourage women from participating to screening programmes.

Self-collected cervico-vaginal samples are not suited for Pap test because of lower specimen quality. Several studies show that Hr-HPV testing on self samples appars at least as sensitive for CIN2+ as cytology or hrHPV detection on clinicial-obtained samples, though often less specific. This specificity reduction can be tackled by application of molecular triage methods, directly on the self-sampled specimens, to select women that need colposcopy. HPV genotyping is a suggested method to triage HPV positive women. Initial data suggested that methylation status of human (CADM1,MAL19) or miRNAs (hsa-miR-124-2) as promising tool to triage HPV positive women, but available evidences are very far from what needed for clinical application Moreover HPV DNA includes a total of 113 CpGs that could be potentially methylated , reflecting mechanistically relevant events for cervical carcinogenesis.

Available data regarding Self-HPV studies have been generated from samples collected with standard "wet" transport media while few studies offered dry-swabs,developed more recently. Acceptability studies for Self-HPV indicate that the method is generally well accepted by women, but revealed that some of women have doubts about the validity of the method. One of these was the concern about manipulating the test tube and spilling out the transport medium during the sampling procedure, which some patients interpreted as incorrect and feared that it might affect the test result ... The aims of the present study are 1) to assess the effects of a hrHPV self-sampling test as strategies to reach non-attending women in organized cervical screening in comparison with standard recall by letter in 8000 women 2) To evaluate the performance of two self sampling devices with and without a preservative buffer and to explore their acceptability amiong invited women 3) To evaluate a molecular triage approach for management of HPV positive women in self sampling collected material by HPV genotyping and DNA methylation marker panel.

8. SPECIFIC AIMS (Max 2500 Characters)

The aims of the study are:

- To assess the effects of a hrHPV self-sampling test as strategies to reach non-attending women in organized cervical screening. In four different areas of Tuscany Region, where the HPV-primary test has been implemented in women aged 34-64, we will identify women who had not had any cervical smears taken for > 3 years . These women will be randomized in two groups in order to evaluate the response to invitation to a self obtained vaginal sample for hr-HPV infection testing in comparison to the standard written reminder letter .

- To evaluate the performance of two self sampling devices with and without a preservative buffer (wet and dry self sampling device) and to explore their acceptability among invited women. Acceptability studies for Self-HPV indicate that the method is generally well accepted by women, but revealed that women doubt about the validity of the method and that 50%-70% of women worry they will not take the sample properly. One of the reasons for concern was the manipulation of the test tube and spilling out the transport medium during the sampling procedure. Women feared their practice could affect the test result.

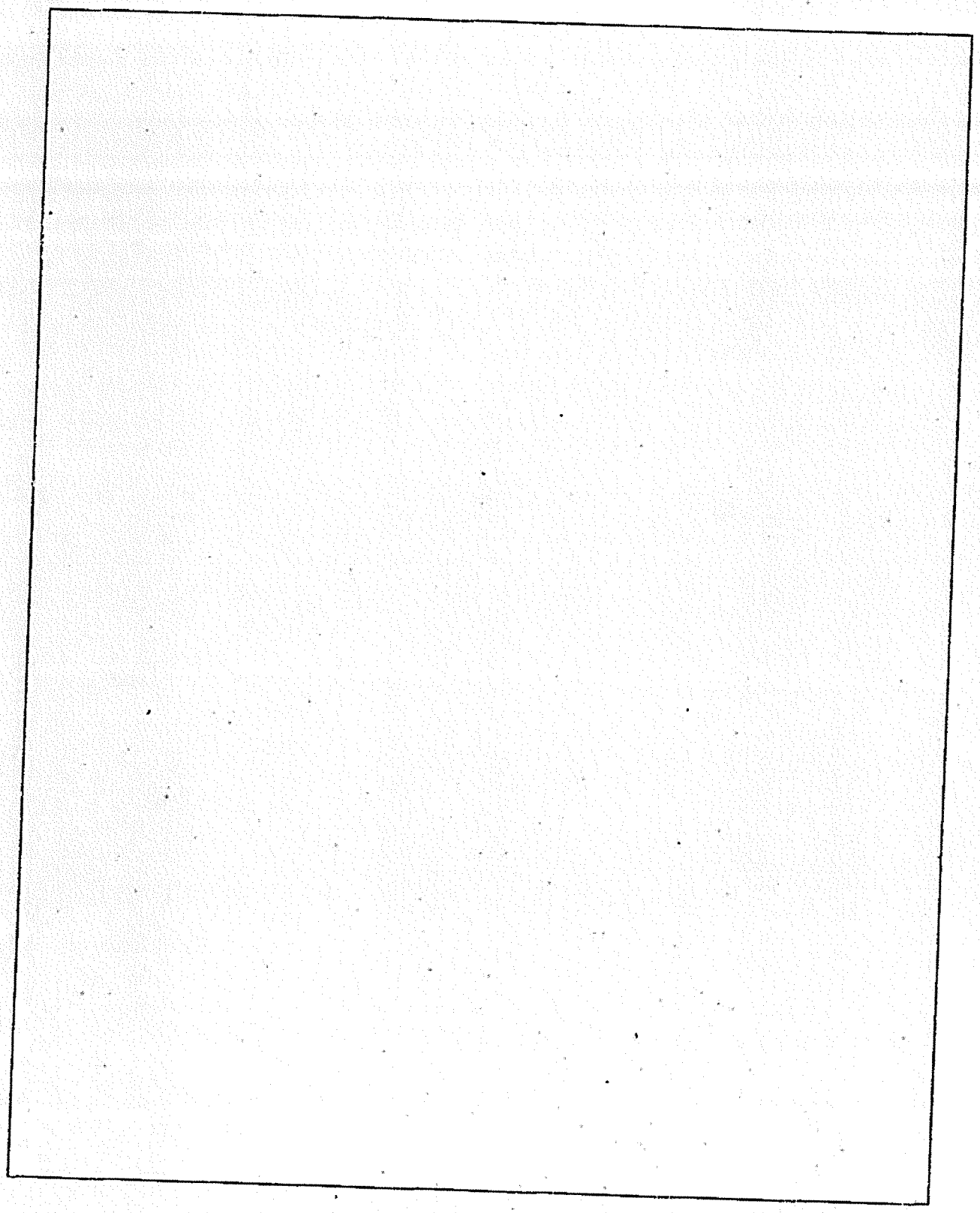
- To assess a molecular triage approach for management of HPV positive women in self sampling collected material. HPV genotyping and DNA methylation marker panel will be used . Currently no system of self sampling collection allows the preservation of cell morphology and therefore it is not possible to perform Pap test or immuno-cytochemistry after HPV positive results according to the routine screening protocol with HPV as primary screening test. This part of the project will allow to determine whether a molecular triage can replace the Pap test triage in self –collected specimens . All HPV positive women will be referred immediately to colposcopy and the results of the assessment will be compared in terms of sensibility, specificity and referral rate to results obtained with methylation panel (MAL-1, CADM1, hsa-miR-124-2 and methylation status of viral genes L1 and L2) and genotyping with the ones from self-sampling material.

9. BACKGROUND AND RATIONALE (Max 4000 Characters)

In Italy cervical cancer screening programmes cover about two-thirds of the female population aged 25–64 years; Pap Test every 3 years was the primary screening test until 2013. After the demonstration that a HPV screening is more effective than screening based on cytology in preventing invasive cancers of the uterine cervix (Ronco G et al), the Italian Ministry of Health in 2013 supported the implementation of HPV as primary test in screening program. So, the Tuscany Region stated HPV test is the new primary screening test for cervical cancer in the age group 34-64 y with the centralization of molecular HPV testing in one laboratory in ISPO. In Tuscany the compliance with invitation for cervical cancer screening was 56% and more than 67% of invasive cancer occurs in never screened women or under-screened women.

In fact in most industrialised countries, the majority of invasive cancers occurs in never-screened or under-screened women. So, the heaviest and most immediate impact on cervical cancer prevention can be obtained only by improving the test coverage. A recently introduced approach involves the use of self-collected cervico-vaginal material as an alternative for clinician-collected samples. Several studies show that Hr-HPV testing on self samples appears at least as sensitive for CIN2+ as cytology or hrHPV detection on clinician-obtained samples, though less specific. So the use of HPV DNA test as primary screening test allows for the introduction of self-sampling (Snijeder 2013, Oscarsson et, Gök M et al, Sanner K et al), as a good alternative to facilitate the screening of women who are reluctant to participate in current screening programs. Acceptability data regarding Self-HPV studies have been generated from samples collected with standard "wet" transport media and the method is generally well accepted by women, but revealed that some of women have doubts about the validity of the method. One of these was the concern about manipulating the test tube and spilling out the transport medium during the sampling procedure, which some patients interpreted as incorrect and feared that it might affect the test result [Quiao et al, Lazcano-Ponce E]. This is an important issue, because it might lead to lower participation rates using Self-HPV. To address the acceptability and the confidence of women with the self-sampling devices, we will use two self-HPV methods: a Self-HPV dry swabs and a Self-HPV wet with a transport medium. Small studies suggest that HPV tests sampled by physicians using dry vaginal swabs are as accurate as those performed with standard transport medium for HPV detection.

One important aspect to evaluate introducing HPV test by self-sampling is the management of HPV positive women. In HPV screening programs, HPV-positive women are not to be directly referred to colposcopy but Pap Test triage is performed and only women with abnormal PAP test are sent to colposcopy. Since cyto-morphology on self-sampled specimens is not an option, women who tested hrHPV-positive are recalled to perform a Pap smear or colposcopy (Gok 2010, Gok 2012), which is unlikely to be effective in already non-responders. Application of a molecular triage testing directly on the self-sampled specimens would be an ideal alternative to select women that need colposcopy. HPV16/18 genotyping is a proposed triage strategy for hrHPV-positive women with normal cytology and the sensitivity and specificity for CIN3 are not optimal. We will evaluate not only HPV 16/18 genotyping but all HR HPV genotyping . Initial data suggested that methylation status of human or viral genes and miRNAs as promising tool to triage HPV positive women, but available evidences are very far from what is needed for clinical application. Methylation of CpG islands within promoter regions of genes and microRNAs such as CADM1, MAL, and hsa-miR-124-2, reflects mechanistically relevant events for cervical carcinogenesis [Kanna et al, Holanda et al, Igidbashian S et al , Snijeders et al 2013]. Moreover the HPV DNA includes a total of 113 CpGs that could be potentially methylated. Several studies, mostly based on small number of samples, showed different patterns of HPV DNA methylation in cervix cancer and precancerous cervical lesions compared to cervical cells with transient HPV infection. Pilot studies have shown that the detection of promoter hypermethylation of genes involved in cervical carcinogenesis is practicable in self-collected lavage specimens and allows the detection of cervical neoplasia (Eijsink JJ et al). Moreover it could be evaluate if methylation status work at the same way for all HPV types and what it adds to HPV specific genotyping.



10. RESEARCH PLAN (Max 5 pages including figures and/or tables- dimensione del *font* 10 o più)

Setting

The study will be performed in the Tuscany Region including four organised screening programmes : Florence, Viareggio, Grosseto and Carrara. In these areas, cervical screening programmes actively invite all the resident female population aged 34–64 years for HPV test as primary screening test (Florence, Viareggio and Grosseto), according to the new protocol for cervical cancer screening in Tuscany Region, or Pap-test every 3 years (Carrara) .

Study population

Women aged 34–64 years who had been invited by the screening programme in the previous round of screening and had failed to respond for at least 3 years will be eligible for mail recall.

In the 4 involved screening programs , every year about 63.000 in the age class 34-64 years are invited to participate at the screening program and about 40% of women do not responded to the invitation of the program .

Study design

The lists of eligible women will be provided to ISPO by the involved screening programs (Viareggio, Carrara, Grosseto and Florence; for Florence ISPO is already in charge to enrol directly the women for the screening programs).Out of them , 8000 eligible women consecutively selected from the lists will be randomised in two groups. The aim is to evaluate the response rate to invitation to a self obtained vaginal-cervical sample for hr-HPV infection testing in comparison to the standard written reminder letter. Randomisation will be performed centrally by the coordinating centre (ISPO) using computer generated random numbers. In the first year a random sample of 4000 eligible women from the 4 screening programs will be invited to participate in the study sending self sampling at home.

In the control arm , the women will receive the usual recall with a new invitation letter with a prefixed appointment (it can be moved with a phone call) to perform HPV screening test in the local districts or clinic.

In the intervention arm selected to receive self sampling at home, we will allocate randomly the women to 2 different self sampling devices differing in having or not a preservative buffer (.

So the group of women allocated in the intervention arm (4000) will be further randomized 1:1 for receiving S-wet or S-dry device .

Assuming that the compliance for the traditional method with an invitation letter is equal to 15% (Giorgi Rossi 2010), the present study is designed to be able to detect an absolute difference of 1.5% or greater in the attendance rate with a conventional levels of power (80%) and significance (95%, one side test) with a planned sample size of 8000 women.

Assuming a sample size equal to 2000 women for each sampling devices, a significant difference equal to or greater than 4.0 percentage points more or less , considering a HPV positive rate of about 21% (Giorgi Rossi 2010) with same power and significance.

The study will be submitted , before starting, for approval to the Coordinating Center and Area Vasta Local Ethical Committees.

Each women in the study groups will receive an alerting letter explaining that the local Public Screening Program would provide her with a box containing a self-sampler device completely free of charge to perform self- HPV screening test directly at home . After 1 week, each screening program involved in the study will ship by regular mail at home of the randomised women a letter of invitation to participate in the HPV screening program and a box with: self-sample sampling device, a HPV screening leaflet in use in Tuscany Region Program. Information related to the study, instructions to perform self-sampling, pre-printed labels to put on the tube, the informed consent form to sign , the questionnaire and a pre-stamped envelope to return the self-sampling kit.

Special videos explaining how to perform sample sampling will be prepared and posted on you-tube, one for each type of self sampling device and the link will be written in the invitation letter.

Questionnaires will be send with self-sampling device including items related to: date of women's latest Pap-test, questions about the self-sampling performance (pain, embarrassment, feasibility), what was

mostly appreciated in the self-sampling (doing it by themselves, privacy, absence of a doctor, absence of speculum) and what they did not like regarding self-sampling (pain, the device, the instruction). All information will be collected using 5-point ordinal scales on the general acceptability.
Women that decide to participate in the study can send directly by regular mail to the local screening program the pre-stamped envelope with the self-sampling, the questionnaire and the signed informed consent (which will also include the authorization for telephone contact).
In second year of study in the city of Florence we will also evaluate the possibility to involve Drugstores in the distribution of self-sampling. In this case 500 randomised women will be invited by letter to perform self sampling for HPV screening test collecting the device in the drugstore. A list of drugstores which agreed to be included in the study will be available in the invitation letter. The impact on compliance and satisfaction of women will be evaluated.

All HPV analysis and molecular tests will be performed in Molecular Laboratory of ISPO , the central lab for HPV screening test in Tuscany Region

HR-HC2 testing
Samples collected with S-Wet self sampling device will be centrifuged at 500 g for 10 min. Supernatants will be discarded and pellets suspended in 1ml of STM (Specimen Transport Medium; Qiagen, Hilden, Germany). Before performing Hr-Hybrid Capture 2 (HC2), 200 µl aliquots will be stored at -80°C.
Samples collected with S-DRY: In the laboratory 1ml of 0.9% normal saline will be added and each tube was vortexed for 30 s before removing and discarding the swab collection devices. A volume of 0.5 ml will be removed and used for denaturation into the Digene hybrid capture 2 [hc2] assay.
HPV will be evaluated with the same HPV test used in regular screening: HC2 (Qiagen), using only the B probe mix, which is specific for 12 HR HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and one probably carcinogenic HPV type: 68. The recommended positivity threshold of 1pgml_1 (equivalent to 5000 viral copies per test well) will be used as a cutoff control value, and all samples with an RLU/Control ratio 1.00 were considered HR-HPV positive.
All HC2-negative samples will be further analysed to evaluate sample adequacy. DNA will be extracted from 200 µl of un-denaturated STM samples with QIAamp DNAMini kit (Qiagen) according to the manufacturer's instruction. Amplification of the human b-globin gene will be performed using GH20-PC04 primers (268-bp amplicon length) (Bauer et al, 1992).

Management of enrolled women
HPV negative women will receive at home the results of the screening test and they are re-invited after 5 years according to the HPV screening protocol.
All women who resulted in being HPV positive will be contacted by phone to perform colposcopy and a counselling on HPV and cervical cancer risk. If the colposcopy will be positive, a biopsy will be taken, and each women will be followed according to the protocol of HPV screening program in Tuscany. If colposcopy will be negative, women will be re-invited to undergo control with HPV test within a year's time. During colposcopy also a Pap test will be taken to guide the post colposcopic follow-up according to the protocol approved in Tuscan Region. If a woman with hr-HPV did not attend, efforts were made to contact her again by phone and then also by letter

Molecular Triage of HPV positive women
HPV Genotyping :
Specific genotyping will be performed in all HC2-positive samples. DNA will be extracted from 200 µl of un-denaturated STM samples with QIAamp DNAMini kit (Qiagen) according to the manufacturer's instruction. Genotyping will be perfomed using a validate low-cost PGMY-based PCR assay (PGMY-CHUV) for the genotyping of 31 HPV types by reverse blotting hybridization (RBH).This genotyping method is published in the first WHO HPV Laboratory manual (UngerE. R. et al) and ISPO laboratory perfoms it from several years.

In all HPV positive self-collected samples we will perform quantitative methylation analyses in order to obtain a quantification for the methylation status of the investigated CpGs, using DNA extracted for genotyping. We will evaluate Methylation of CpG islands within promoter regions of genes and microRNAs such as CADM1, MAL, and hsa-miR-124- and Methylation status of the HPV regions L1 and L2. We will investigate for each type the CpGs located nearby the sequence position of HPV16 CpGs which have been highlighted as associated with an increased risk of CIN2+: L1 nucleotide positions 5601-5616 and 6457; L2 nucleotide position 4261

Bisulfite modification: Genomic DNA samples will undergo bisulfite modification using the commercial EZ DNA Methylation Kit (Zymo Research). The bisulfite-modified genomic DNA will be re-suspended in 1X TE buffer and used immediately for pyrosequencing or stored at –80°C. Human synthetic methylated and unmethylated DNA controls for human genes and DNA from CaSki cell line or a WHO HPV16-DNA control for viral genes will be included in each modification set to check modification efficiency.

Methylation status: Methylation status in the selected genes will be evaluated on the bisulfite modified DNA The assays will be performed employing primers selected according to published sequences (Hesselink AT et al. Mirabello L et al, Wentzensen N et al). When not available, primers will be designed using a specific software . Links with available Gene-banks will be set up for gene sequence references

A preliminary PCR reaction will be performed in a total volume of 35 microL containing 1X KCl, 2 mM MgCl2 , 200 microM dNTPs, 0.5 microM of each primer (antisense biotinylated), 1.75U Taq polymerase and 6 microL modified DNA with the proper thermocycling profile. Amplification and real-time measurement was performed in the 7500 ABI system (Applied Biosystems, Foster City, CA, USA). A Mathematical model for relative quantification in real-time PCR will be applied to determine the relative quantification of a target gene in comparison to a reference gene (Pfaffl MW).

Bisulfite modified controls for methylated and unmethylated status of cell and viral gene respectively will be included in each run

Genotyping and MSP results will be correlated in terms of sensitivity and specificity to histological outcome and follow-up results in HPv positive women with and without clinically meaningful cervical disease diagnosed within a two-year follow-up period

<u>Role of each Unit involved in the study and timeline</u>

In the first year of the study ISPO will randomise women , send the randomisation list to each screening centers, set up the study data base and the software computer validation. The boxes and all materials for the mailing of self sampling devices will be prepared.

Each screening center will invite women, will send the box with self sampling device, receive the self sampling device from the invited women, register them in the database, send the samples to ISPO Central Lab . Ispo Lab will perform hr-HPV testing and send the results to each screening center.

Each screening center will receive the Hr-HPV results from ISPO and send them to the woman . In case of HPV positive results the local screening center will contact the woman by phone for colposcopic assessment, perform colposcopy and every further follow-up visits, record the results and questionnaires data in the data base and participate in evaluation of the results.

In the second year ISPO will evaluate the feasibility to distribute the self sampling using pharmacies and invited women for this purpose perfoming hr-HPV test for responding women.. ISPO will perform also HPV typing and methylation profiles, will records all data in the data base of the study , perform statistical analysis and evaluation of the results.

11. PRELIMINARY RESULTS (Max 2 pages including figures and/or tables- dimensione del *font* 10 o più)

From 2012 Tuscany HPV test is the new primary screening test for cervical cancer and it replaced the traditional Pap test in the age group 34-64 y. The implementation of the new program is gradual by ASL (Local Health Unit) and Age. The program will be fully operative in three years in all ASL of the Tuscany Region.

Currently (Dec 2013) it has been implemented in Florence and in the other 2 Cities (Grosseto and Viareggio). The Tuscany HPV program provides the centralization of molecular HPV testing in the laboratory located in ISPO (Center for research and Cancer Prevention).

So there is already in place a strong collaboration between ASL Viareggio, ASL Grosseto and ISPO with a system for samples shipment and communication of the results.

11a) FEASIBILITY (Max 2.000 characters)

From 2012 Tuscany HPV test is the new primary screening test for cervical cancer and it replaced the traditional Pap test in the age group 34-64 y. The implementation of the new program is gradual by ASL (Local Health Unit) and Age. The program will be fully operative in three years in all ASL of the Tuscany Region.

Currently (Dec 2013) it has been implemented in Florence and in the other 2 Clties (Grosseto and Viareggio). The Tuscan HPV program provides the centralization of molecular HPV testing in one laboratory located in ISPO (Center for research and Cancer Prevention).

So there is already in place a strong collaboration between ASL Viareggio, ASL Grosseto and ISPO with a system for samples shipment and communication of the results.

Ispo particlpated in several randomised trial including NTCC Trial (New Technologies for Cervical Cancer screening); this study provided a large amount of new information on HPV-based screening and, in particular, showed that it allows earlier detection of hgCIN than cytology and provides greater protection against invasive cervical cancer1. Until the end of 2013 NTCC had directly produced 19 articles with an overall impact factor of 190.29 and 1286 citations (source Google Scholar) until the end of 2013. Ispo participated also in a previous small Italian trail evaluating self-sampling in a ascreening setting, and ISPO laboratory coordinated all molecular analysis and their protocols.

All the four Tuscan screening Centers (Carrara, Viareggio, Grosseto and Florence) are a large experience in enrolling women within screening program.

ISPO Unit of cancer Epidemiology 2 has local computer network with large memory availability, Software for data management and statistical analyses.

Analytic Cytology and Biomolecular Unit of ISPO: The Units include laboratories involved in viral oncology and molecular analyses for characterization of different tumors and pathogenetic pathways; a group is involved on studies on HPV in cervical, anal and oropharyngeal cancers. The Unit has separated pre- and post- PCR rooms. Relevant equipment includes five PCR thermocyclers, ABI 310 Genetic Analyzer, horizontal apparatus for gel electrophoresis, one UV transilluminator, two Miniblotters for in-house RBH,a dark room, a developer processor, Auto-Lipa automatic system for HPV genotyping, instruments for real-time PCR and for sequencing and pyrosequencing, six refrigerators at 4°C, six at -20°C and six at -80°C. It has also full equipment to perform hr-HPV testing validated for screening purpose.

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13. PERSONEL INVOLVED IN THE RESEARCH PROJECT - P.I.'S UNIT AND ADDITIONAL UNITS (IF ANY)

FIRST AND LAST NAME	Position	Project Role	Dedicated Time (%)
Francesca Carozzi	Biologist, Leader-ISPO	Principal Investigator	20%
Massimo Confortini	Biologist, Director U.O – ISPO	Supervisor	5%
Cristina Sani	Biologist, ISPO	Lab analysis, organization of the study, data collection	10%
Simonetta Bisanzi	Biologist, ISPO	Lab analysis and organization of the study,	5%
To be appointed	Fellowship	Organization, Lab analysis, data entry	100%
Carmela di Pierro	Midwife ISPO	Enrolment, counselling and Cervical samples	10%
Marco Zappa	Medical Doctor, Epidemiologist – ISPO	Data collection, data Analysis	2%
Paola Mantellini	Medical Doctor, Director of CRR and screening Unit- ISPO	Organization and analysis	5%
Anna Iossa	Medical Doctor, Gynaecologist ISPO	Organization of recruitment and local shipment , Training of local health unit staff.	10%
Aurora Assunta Scarfantoni	Biologist ASL 12 Viareggio – Additional Unit	PI Additional Unit Organization of recruitment, Training of local health unit staff , Evaluation of results	15%
To be appointed	Fellowship- Additional Unit ASL 12 Viareggio	Organization support, recruitment , data entry	100%
Cristina Nicolai	Biologist – Additional Unit ASL 1 Carrara	PI Additional Unit Organization of recruitment, , Training of local health unit staff , Evaluation of results	15%
To be appointed	Fellowship- Additional Unit ASL 1 Carrara	Organization support , recruitment , data entry	100%
Roberta Rosati	Medical Doctor Additional Unit ASL 9 Grosseto	PI Additional Unit Organization of recruitment, , Training of local health unit staff , Evaluation of results	15%
To be appointed	Fellowship- Additional Unit ASL 9 Grosseto	Support in the Organization, recruitment , data entry	100%
Karin Andersson	Gynaecologist , ISPO	Colposcopy and Follow-up of women	5%
Alessandro Ghelardi	Gynaecologist, ASL 1	Colposcopy and Follow-up of women	5%

Patrizia Falini	Statistician, ISPO	Recruitment, randomisation and statistical analysis	5%
Donella Puliti	Statistician, ISPO	Recruitment, randomisation and statistical analysis	5%
Stefania Capassoni	Nurse -ISPO-	Enrolment, counselling and Cervical samples	5%

14. CURRICULUM VITAE (Principal Investigator) (Max 4000 Characters)

Curriculum vitae Francesca Maria Carozzi

Born in Carrara on September 11th 1956, graduated in Biology at Pisa University in 1980 and specialized in General Pathology in 1984, in Cytochemistry and Istochemistry (Univ. Pavia, 1986) and Biomecular techniques (Univ. Milan 1993).

She has worked from 1989 at the Centro per lo Studio e la Prevenzione Oncologica of Florence in department of Cytology and Molecular Unit. Her main fields of interest are cervix, colorectal, lung and prostate cancer screening, She experience in molecular biology especially on the evaluation of new molecular methods for screening and related fields

Dr Carozzi's research interest are mainly the development of sensitive molecular biology techniques and their application for the early detection of breast , lung and colorectal cancer. She has been involved in the NTCC trial, a multi-centre randomised trial for the evaluation of new methods for cervical cancer screening, as responsible for molecular HPV testing and supervisor the interlaboratory quality assurance for HC2. Member of International (US/EU) cooperative working group to evaluate strategies for early detection of lung cancer .

Responsible of biobank related to laboratory unit, a structure integrated and centralized for the collection and storage of biological samples in clinical trials, in research projects or for which storage is required by law; Since June 2007, she participated in the work of the WHO Global HPV Labnet group to analyze the laboratory related to the introduction, follow-up and monitoring of HPV vaccines. She was nominated several times as reviewer of European projects within FP6, FP7 call and Eu-Africa call.

Author of several papers published on national/international scientific journal and presentation in national/International congresses. H index 19;

15. SELF EVALUATION FORM (Principal Investigator)

Total Papers and Reviews with IF (from January 2008 or last available)	30
Total IF (from January 2008 or last available)	166,03
Average IF	5,53

Total Papers First/Last Author with IF (from January 2008 or last available)	11
Total IF (from January 2008 or last available)	79,729
Average IF	7,24

15.1 LIST OF PAPERS WITH IF (FROM JANUARY 2008) OF THE PRINCIPAL INVESTIGATOR

Carozzi F, Confortini M, Dalla Palma P e, Del Mistro A, Gillio-Tos A, De Marco L, Giorgi-Rossi P, Pontenani G, Rosso S, Sani C, Sintoni C, Segnan N, Zorzi M, Cuzick J, Rizzolo R, Ronco G; New Technologies for Cervival Cancer Screening (NTCC) Working Group. Use of p16-INK4A overexpression to increase the specificity of human papillomavirus testing: a nested substudy of the NTCC randomised controlled trial. Lancet Oncol. Oct;9(10):937-45 2008. IF: 21.856

Carozzi F, Ronco G, Gillio-Tos A, De Marco L, Del Mistro A, Girlando S, Franceschi S, Plummer M,Vaccarella S. Concurrent infections with multiple human papillomavirus (HPV) types in the New Technologies for Cervical Cancer (NTCC) screening study EUROPEAN JOURNAL OF CANCER, vol. 48, p. 1633-1637, 2012 IF: 5.257

Carozzi F, Gillio-Tos A, Confortini M, Del Mistro A, Sani C, De Marco L, Girlando S, Rosso S, Naldoni C, Dalla Palma P, Zorzi M, Giorgi-Rossi P, Segnan N, Cuzick J, Ronco G; NTCC working group. Risk of high-grade cervical intraepithelial neoplasia during follow-up in HPV-positive women according to baseline p16-INK4A results: a prospective analysis of a nested substudy of the NTCC randomised controlled trial. Lancet Oncol. Feb;14(2):168-76. 2013 IF: 21.856

Carozzi F, Visioli CB, Confortini M, Iossa A, Mantellini P, Burroni E, Zappa M. hr-HPV testing in the follow-up of women with cytological abnormalities and negative colposcopy. Br J Cancer. Oct 1;109(7):1766-74. 2013 IF 5,08

Carozzi FM, Bisanzi S, Falini P, Sani C, Venturini G, Lopes Pegna A, Bianchi R, Ronchi C, Picozzi G, Mascalchi M, Carrozzi L, Baliva F, Pistelli F, Tavanti L, Falaschi F, Grazzini M, Innocenti F, Paci E; ITALUNG Study Research group... Molecular profile in body fluids in subjects enrolled in a randomised trial for lung cancer screening: Perspectives of integrated strategies for early diagnosis. Lung Cancer. May;68(2):216-21 2010 IF 3,457

Carozzi FM, Burroni E, Bisanzi S, Puliti D, Confortini M, Giorgi Rossi P, Sani C, Scalisi A, Chini F. Comparison of clinical performance of Abbott RealTime High Risk HPV test with that of hybrid capture 2 assay in a screening setting J Clin Microbiol. Apr;49(4):1446-51 2011 IF 4,07

Carozzi FM, Tornesello ML, Burroni E, Loquercio G, Carillo G, Angeloni C, Scalisi A, Macis R, Chini F, Buonaguro FM, Giorgi Rossi P; HPV Prevalence Italian Working Group. Prevalence of human papillomavirus types in high-grade cervical intraepithelial neoplasia and cancer in Italy.Cancer Epidemiol Biomarkers Prev. 2010 Sep;19(9):2389-400. IF 4,559

Giorgi Rossi P, Chini F, Bisanzi S, Burroni E, Carillo G, Lattanzi A, Angeloni C, Scalisi A, Macis R, Pini MT, Capparucci P, Guasticchi G, Carozzi F. Distribution of high and low risk HPV types by cytological status: a population based study from Italy INFECTIOUS AGENTS AND CANCER, 2011, vol. 6, p. 2-10. IF: 1.94

Burroni E, Bisanzi S, Sani C, Puliti D, Carozzi F. Codon 72 polymorphism of p53 and HPV type 16 E6 variants as risk factors for patients with squamous epithelial lesion of the uterine cervix. J Med Virol. Jan;85(1):83-90. 2013 F: 3.120

Giorgi Rossi P, Marsili LM, Camilloni L, Iossa A, Lattanzi A, Sani C, Di Pierro C, Grazzini G, Angeloni C,

Capparucci P, Pellegrini A, Schiboni ML, Sperati A, Confortini M, Bellanova C, D'Addetta A, Manla E, Visioli CB, Sereno E, Carozzi F. The effect of self-sampled HPV testing on participation to cervical cancer screening in Italy: a randomised controlled trial (ISRCTN96071600). BRITISH JOURNAL OF CANCER, vol. 104 , p. 248-254 2011. IF: 5.042

Levi M, Bonanni P, Burroni E, Bechini A, Boccalini S, Sani C, Bonaiuti R, Indiani L, Azzari C, Lippi F, Carozzi F, Working Group TH. Evaluation of bivalent human papillomavirus (HPV) vaccine safety and tolerability in a sample of 25 year old Tuscan women. Hum Vaccin Immunother. Apr 9;9(7) 2013. IF: 3.492

Donati S, Giambi C, Declich S, Salmaso S, Filia A, Ciofi degli Atti ML, Allbrandi MP, Brezzi S, Carozzi F, Collina N, Franchi D, Lattanzi A, Meda M, Minna MC, Nannini R, Gallicchio G, Bella A, PreGio Working group. Knowledge, attitude and practice in primary and secondary cervical cancer prevention among young adult Italian women. VACCINE 2012, vol. 30, p. 2075-2082. IF: 3.766

Giambi C, Donati S, Declich S, Salmaso S, Degli Atti ML, Allbrandi MP, Brezzi S, Carozzi F, Collina N, Franchi D, Lattanzi A, Meda M, Minna MC, Nannini R, Scherillo I, Bella A, PreGio Working Group Estimated acceptance of HPV vaccination among Italian women aged 18-26 years. VACCINE 2011, vol. 29, p. 8373-8389. IF: 3.766

Ronco G, Biggeri A, Confortini M, Naldoni C, Segnan N, Sideri M, Zappa M, Zorzi M, Calvia M, Accetta G, Giordano L, Cogo C, Carozzi F, Gillio Tos A, Arbyn M, Meijer CJ, Snijders PJ, Cuzick J, Giorgi Rossi P. Health technology assessment report: HPV DNA based primary screening for cervical cancer precursors. EPIDEMIOLOGIA E PREVENZIONE 2012, vol. 36, p. 1-72. IF: 0.91

Accetta G, Biggeri A, Carreras G, Lippi G, Carozzi FM, Confortini M, Zappa M, Paci E. Is human papillomavirus screening preferable to current policies in vaccinated and unvaccinated women? A cost-effectiveness analysis. J Med Screen. 2010;17(4):181-9. IF 2,354

Baussano I, Elfström KM, Lazzarato F, Gillio-Tos A, De Marco L, Carozzi F, Del Mistro A, Dillner J, Franceschi S, Ronco G. Type-specific human papillomavirus biological features: validated model-based estimates. PLoS One. 2013 Nov 29;8(11) IF 3,73

Baussano I, Franceschi S, Gillio-Tos A, Carozzi F, Confortini M, Dalla Palma P, De Lillo M, Del Mistro A, De Marco L, Naldoni C, Pierotti P, Schincaglia P, Segnan N, Zorzi M, Giorgi-Rossi P, Ronco G. Difference in overall and age-specific prevalence of high-risk human papillomavirus infection in Italy: evidence from NTCC trial. BMC Infect Dis. 2013 May 24;13(1):238.. IF: 3.03

Confortini M, Carozzi F, Zappa M, Ventura L, Iossa A, Cariaggi P, Brandigi L, Franchini M, Mirri F, Viacava P, Scarfantoni A, Bazzanti D, Sani C. Human papillomavirus infection and risk factors in a cohort of Tuscan women aged 18-24: results at recruitment BMC Infect Dis. 2010 Jun 7;10:157. IF: 2,55

Field JK, van Klaveren R, Pedersen JH, Pastorino U, Paci E, Becker N, Infante M, Oudkerk M, de Koning HJ; European Randomized Screening Trial Group. European randomized lung cancer screening trials Post NLST. J Surg Oncol. 2013 Oct;108(5):280-6. IF 2,644

Giambi C, Donati S, Carozzi F, Salmaso S, Declich S, Atti ML, Ronco G, Allbrandi MP, Brezzi S, Collina N, Franchi D, Lattanzi A, Minna MC, Nannini R, Barretta E, Burroni E, Gillio-Tos A, Macaillini V, Pierotti P, Bella A. A cross-sectional study to estimate high-risk human papillomavirus prevalence and type distribution in Italian women aged 18-26 years. BMC Infect Dis. 2013 Feb 7;13:74.. IF: 3.03

Gillio-Tos A, De Marco L, Carozzi FM, Del Mistro A, Girlando S, Burroni E, Frayle-Salamanca H, Giorgi Rossi P, Pierotti P, Ronco G; New Technologies for Cervical Cancer Screening Working Group. Clinical impact of the analytical specificity of the hybrid capture 2 test: data from the New Technologies for Cervical Cancer (NTCC) study. J Clin Microbiol. 2013 Sep;51(9):2901-7.. IF 4,07

Giorgi Rossi P, Carozzi F, Collina G, Confortini M, Dalla Palma P, De Lillo M, Del Mistro A, Ghiringhello B, Gillio-Tos A, Maloli P, Pellegrini A, Schiboni ML, Segnan N, Zaffina LM, Zorzi M, Ronco G. HPV testing is an efficient management choice for women with inadequate liquid-based cytology in cervical cancer screening. AMERICAN

JOURNAL OF CLINICAL PATHOLOGY 2012, vol. 138, p. 65-71, IF: 2.6

Giorgi Rossi P, Chini F, Borgia P, Guasticchi G, Carozzi FM, Confortini M, Angeloni C, Buzzoni C, Buonaguro FM; Gruppo di lavoro HPV Prevalenza. Human Papilloma Virus (HPV), cervical cancer incidence and screening uptake: differences among Northern, Central and Southern Italy .Epidemiol Prev. 2012 Mar-Apr;36(2):108-19. Review. Italian. IF 0,91

Lopes Pegna A, Picozzi G, Mascalchi M, Maria Carozzi F, Carrozzi L, Comin C, Spinelli C, Falaschi F, Grazzini M, Innocenti F, Ronchi C, Paci E; ITALUNG Study Research Group. Design, recruitment and baseline results of the ITALUNG trial for lung cancer screening with low-dose CT. Lung Cancer. 2009 Apr;64(1):34-40.. IF 3,457

Mangoni M, Bisanzi S, Carozzi F, Sani C, Biti G, Livi L, Barletta E, Costantini AS, Gorini Association between genetic polymorphisms in the XRCC1, XRCC3, XPD, GSTM1, GSTT1, MSH2,G. MLH1, MSH3, and MGMT genes and radiosensitivity in breast cancer patients. INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY BIOLOGY PHYSICS 2011, vol. 81, p. 52-58. IF: 4.764

Lopes Pegna AL, Picozzi G, Falaschi F, Carrozzi L, Falchini M, Carozzi FM, Pistelli F, Comin C, Deliperi A, Grazzini M, Innocenti F, Maddau C, Vella A, Vaggelli L, Paci E, Mascalchi M; for the ITALUNG Study Research Group. Four-Year Results of Low-Dose CT Screening and Nodule Management in the ITALUNG Trial. J Thorac Oncol. 2013 Jul;8(7):868-875.. IF: 3.661

Ronco G, Giorgi-Rossi P, Carozzi F, Confortini M, Dalla Palma P, Del Mistro A, Gillio-Tos A, Minucci D, Naldoni C, Rizzolo R, Schincaglia P, Volante R, Zappa M, Zorzi M, Cuzick J, Segnan N; New Technologies for Cervical Cancer Screening Working Group. Results at recruitment from a randomized controlled trial comparing human papillomavirus testing alone with conventional cytology as the primary cervical cancer screening test. J Natl Cancer Inst. 2008 Apr 2;100(7):492-501.. IF 14.336

Ronco G, Giorgi-Rossi P, Carozzi F, Confortini M, Dalla Palma P, Del Mistro A, Ghiringhello B, Girlando S, Gillio-Tos A, De Marco L, Naldoni C, Pierotti P, Rizzolo R, Schincaglia P, Zorzi M, Zappa M, Segnan N, Cuzick J; New Technologies for Cervical Cancer screening (NTCC) Working Group. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. Lancet Oncol. 2010 Mar;11(3):249-57. IF21.856

Rossi PG, Sideri M, Carozzi F, Vocaturo A, Buonaguro FM, Tornesello ML, Burroni E, Mariani L, Boveri S, Zaffina LM, Chini F. HPV type distribution in invasive cervical cancers in Italy: pooled analysis of three large studies. INFECTIOUS AGENTS AND CANCER 2012, vol. 7, p. 26-37. IF: 3.17

Sali L, Grazzini G, Carozzi F, Castiglione G, Falchini M, Mallardi B, Mantellini P, Ventura L, Regge D, Zappa M, Mascalchi M, Milani S. Screening for colorectal cancer with FOBT, virtual colonoscopy and optical colonoscopy: study protocol for a randomized controlled trial in the Florence district (SAVE study). Trials. 2013 Mar 15;14:74 IF: 2.21

15.2 LIST OF PAPERS WITH IF (FROM JANUARY 2008) OF THE SCIENTIFIC COORDINATOR(S) OF ADDITIONAL RESEARCH UNIT(S -

Confortini M, Carozzi F, Zappa M, Ventura L, Iossa A, Cariaggi P, Brandigi L, Franchini M, Mirri F, Viacava P, Scarfantoni A, Bazzanti D, Sani C. Human papillomavirus infection and risk factors in a cohort of Tuscan women aged 18-24: results at recruitment. BMC Infect Dis. 2010;10:157. 7 IF 3.025

- Giorgi Rossi P, Baiocchi D, Ciatto S; Endocervical Cell Italian Working Group of Cervical Cancer Screening Group. Risk of CIN2 in women with a pap test without endocervical cells vs. those with a negative pap test with endocervical cells: a cohort study with 4.5 years of follow-up. Acta Cytol. 2010;54(3):265-71. IF 0.693

16. FINANCIAL REQUEST

16.1 PRINCIPAL INVESTIGATOR'S UNIT (S)

	Year 1	Year 2	Year 3	Total
A) NON-STAFF PERSONNEL (CONTRACTS, FELLOWSHIPS, ETC). SPECIFY: ORGANIZATION , HPV TESTING ; GENOTYPING AND METHYLATION ANALISIS; SUPPORT TO STATISTICAL ANALYSIS	30.000	40.000		
B) CONSUMABLES SUPPLIES: SELF SAMPLING DEVICES HPV EXTRACTION AND GENOTYPING BYSULFITE MODIFICATION AND METHYLATION STATUS STM TUBE FOR HC2 STAMPS TO SEND SELF SAMPLING DEVICE	33.000	56.000		
C) SMALL EQUIPMENT(S) SPECIFY:	0	0		
D) TRAVEL EXPENSES (MEETINGS, COURSES, ETC.) SCIENTIFIC MEETING, MEETING INTERNAL TO THE STUDY	1.000	1.000		
E) PUBLICATION COSTS. SPECIFY: TRANSLATION IN SEVERAL LANGUAGES OF LETTERS OF INVITATION AND INFORMATION TO TAKE SAMPLES YOU-TUBE VIDEO PREPARATION	3.000	1000		
F) OVERHEAD (MAX 10%)	6.700	9.800		
TOTAL COSTS	73.700	107.800		

16.2 JUSTIFICATION OF EACH ITEM BUDGET (except for overhead)

a) Non-staff Personnel

To prepare box for sending self sampling device at home of women ; to perform dna extraction, genotyping, molecular analysis and support in statistical analysis

b) Consumable supplies

To buy self-sampling devis, stamps to send self sampling at home by regular mal, performing pre-treatment of samples and molecular analisis

c) Small Equipment(s)

d) Travel Expenses (Meetings, Courses, etc.)

To participate in scientific meeting .

e) Publication Costs

To translate in different languages the letter and other documents important to improve the participation also of non italian women; preparation of professional video to post to YOU-Tube

16.3

1° ADDITIONAL UNIT(S) WITHIN REGIONE TOSCANA [redacted]

	Year 1	Year 2	Year 3	Total
A) NON-STAFF PERSONNEL (CONTRACTS, FELLOWSHIPS, ETC). SPECIFY: ORGANIZATION, SELECTION OF WOMEN, ENROLLING WOMEN	5.500			
B) CONSUMABLES SUPPLIES: STAMPS TO SEND SELF SAMPLING DEVICE, LETTERS, DEPLIANTS, SHIPMENT OF SAMPLES TO ISPO	7.640			
C) SMALL EQUIPMENT(S) (MAX 20.000 EUROS). SPECIFY:				
D) TRAVEL EXPENSES (MEETINGS, COURSES, ETC.) SCIENTIFIC MEETING, MEETING INTERNAL TO THE STUDY	500			
E) PUBLICATION COSTS. SPECIFY:				
F) OVERHEAD (MAX 10%)	1.360			
TOTAL COSTS	15.000			

2° ADDITIONAL UNIT(S) WITHIN REGIONE TOSCANA [redacted]

	Year 1	Year 2	Year 3	Total
A) NON-STAFF PERSONNEL (CONTRACTS, FELLOWSHIPS, ETC). SPECIFY: ORGANIZATION, SELECTION OF WOMEN, ENROLLING WOMEN	5.500			
B) CONSUMABLES SUPPLIES: STAMPS TO SEND SELF SAMPLING DEVICE, LETTERS, DEPLIANTS, SHIPMENT OF SAMPLES TO ISPO	7.640			
C) SMALL EQUIPMENT(S) (MAX 20.000 EUROS). SPECIFY:				
D) TRAVEL EXPENSES (MEETINGS, COURSES, ETC.)	500			
E) PUBLICATION COSTS. SPECIFY:				
F) OVERHEAD (MAX 10%)	1.360			
TOTAL COSTS	15.000			

3° ADDITIONAL UNIT(S) WITHIN REGIONE TOSCANA [redacted]

	Year 1	Year 2	Year 3	Total
A) NON-STAFF PERSONNEL (CONTRACTS, FELLOWSHIPS, ETC). SPECIFY: ORGANIZATION, SELECTION OF WOMEN, ENROLLING WOMEN	5.500			
B) CONSUMABLES SUPPLIES: STAMPS TO SEND SELF SAMPLING DEVICE, LETTERS, DEPLIANTS, SHIPMENT OF SAMPLES TO ISPO	7.840			
C) SMALL EQUIPMENT(S) (MAX 20.000 EUROS). SPECIFY:				
D) TRAVEL EXPENSES (MEETINGS, COURSES, ETC.)	500			
E) PUBLICATION COSTS. SPECIFY:				
F) OVERHEAD (MAX 10%)	1.360			
TOTAL COSTS	15.000			

16.4 ADDITIONAL UNIT(S) - JUSTIFICATION OF EACH ITEM BUDGET (except for overhead)

a) Non-staff Personnel

ORGANIZATION OF THE STUDY, SELECTION OF WOMEN, ENROLLING WOMEN

b) Consumable supplies

Stamps for Sending SELF SAMPLING KITS DIRECTLY AT HOME OF INVITED WOMEN AND RELATED DOCUMENT

c) Small Equipment(s)

d) Travel Expenses (Meetings, Courses, etc.)

Participation in a scientific meeting and internal meeting

e) Publication Costs

16.5 TOTAL

	Year 1	Year 2	Year 3	Total
TOTAL COSTS	118.700	107.800		226.500

17. AVAILABLE GRANT(S) CO-FINANCING THE PROPOSAL (Principal Investigator)

Project Title	none
Principal Investigator	
Granting Agency	
Amount Granted (Euros)	
Amount Available for Co-Financing (Euros)	

17.1 AVAILABLE GRANT(S) CO-FINANCING THE PROPOSAL (Additional Research Units)

Project Title	none
Principal Investigator	
Granting Agency	
Amount Granted (Euros)	
Amount Available for Co-Financing (Euros)	

18. SUGGESTED REVIEWERS (MAX 3).

FIRST AND LAST NAME **Pr. Christine CLAVEL-CRAVOISIER**
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FIRST AND LAST NAME: JOSEPH MONSONEGO
POSITION: GYNECOLOGIST
INSTITUTION INSTITUT DU COL
ADDRESS 174 RUE DE COURCELLES
CITY 75017 PARIS
PHONE TÉL: 01 40 54 09 54
E-MAIL JMONSONEGO@WANADOO.FR

FIRST AND LAST NAME: DEBORAH FRENCH
POSITION PROFESSOR
INSTITUTION UNIVERSITY OF ROME LASAPIENZA
ADDRESS VIA DI GROTTAROSSA 1035
CITY ROME
PHONE 06 3377 5304
E-MAIL DEBORAH.FRENCH/AT/UNIROMA1.IT

19. BIO-ETHICAL REQUIREMENTS

Does the proposed research involve:

19.1 HUMAN EXPERIMENTATION YES NO

Human experimentation includes involvement of human subjects and other issues with ethical implications.

If YES, include approval from the competent Ethical Committee (as addendum A). If this is not yet available at time of submission, please sign the statement below. ITT will not allocate funds until the Ethical Committee approval has been obtained.

Date 14 January 2014..... P.I. Signature.....

19.2 ANIMAL EXPERIMENTATION YES NO

The competent Committee has evaluated the proposal.

If YES, include approval from the competent Committee (as addendum A). If this is not yet available at time of submission, please sign the statement below. ITT will not allocate funds until the competent Committee approval has been obtained.

Date ....14 Jan 2014..... P.I. Signature .....

19.3 STATEMENT (fill in only if you have signed YES (n.19.1 and/or 19.2)

I ...Francesca Maria Carozzi .....hereby declare that I will pledge to obtain the approval of the "Ethical Committee" (for Human Experimentation) and /or the approval of the "competent Committee" (for animal experimentation) for the present Proposal (title)... *'The value of HPV DNA testing using self-collected sampling in non-attendees cervical cancer screening and molecular triage strategies on self-sampled material for HPV positive women'*..... before commencing research.

Date...14 January 2014... P.I. Signature .....

20. DECLARATION AND PRIVACY STATEMENT

I hereby certify that all information submitted in the application form is accurate and complete.
I agree that, in accordance with law 196/2003 , the processing of my personal data shall be performed for the following purposes:

1. administrative management of the dossiers;
2. evaluation of the value of the research projects with transmission of the data to the *Italian and non-Italian referees/evaluators;*
3. activities ancillary and/or pursuant to the above;

The communication of personal data for these purposes in not compulsory although refusal to do so, owing to the peculiarity of the relationship between the data and the aim for which it is requested, will render the candidate ineligible for selection/award.

Date ....14 January 2014..... P.I. Signature .....

Allegato "B"

16. FINANCIAL REQUEST

16.1 PRINCIPAL INVESTIGATOR'S UNIT (S) Rimodulazione con assicurazione

	Year 1	Year 2	Year 3	Total
A) NON-STAFF PERSONNEL (CONTRACTS, FELLOWSHIPS, ETC). SPECIFY: ORGANIZATION , HPV TESTING , GENOTYPING AND METHYLATION ANALISIS; SUPPORT TO STATISTICAL ANALYSIS	35.000	40.000		75.000
B) CONSUMABLES SUPPLIES: SELF SAMPLING DEVICES HPV EXTRACTION AND GENOTYPING BYSULFITE MODIFICATION AND METHYLATION STATUS STM TUBE FOR HC2 POSTAL CHARGES TO SEND SELF SAMPLING DEVICE TRANSLATION IN SEVERAL LANGUAGES OF LETTERS OF INVITATION AND INFORMATION TO TAKE SAMPLES YOU-TUBE VIDEO PREPARATION PAPER PUBLICATION PRINT OF POSTERS	15.860,50	11.130		26.990,50
C) OTHER SPECIFY: ASSURANCE	6.112,50			6.112,50
D) TRAVEL EXPENSES (MEETINGS, COURSES, ETC.) SCIENTIFIC MEETING, MEETING INTERNAL TO THE STUDY	1.000	1.000		2.000
E) PUBLICATION COSTS.	500	1.500		2.000
G) OVERHEAD (MAX 10%)	5.727	5.370		11.097
TOTAL COSTS	84.200	59.000		123.200

16.2 JUSTIFICATION OF EACH ITEM BUDGET (except for overhead)

a) Non-staff Personnel

To prepare box for sending self sampling device at home of women ; to perfom dna extraction, genotyping, molecular analysis and support in statistical analysis

b) Consumable supplies

To buy self-sampling devis, stamps to send self sampling at home by regular mail, performing pre-treatment of samples and molecular analisis

c) Small Equipment(s)

d) Travel Expenses (Meetings, Courses, etc.)

To participate in scientific meeting .

e) Publication Costs

To translate in different languages the letter and other documents important to improve the participation also of non italian women; preparation of professional video to post to YOU-Tube.

3.3

1° ADDITIONAL UNIT(S) WITHIN REGIONE TOSCANA ASL Viareggio

	Year 1	Year 2	Year 3	Total
A) NON-STAFF PERSONNEL (CONTRACTS, FELLOWSHIPS, ETC). SPECIFY: ORGANIZATION, SELECTION OF WOMEN, ENROLLING WOMEN	5.500			5.500
B) CONSUMABLES SUPPLIES: STAMPS TO SEND SELF SAMPLING DEVICE, LETTERS, DEPLIANTS, SHIPMENT OF SAMPLES TO ISPO	3.600			3.600
C) SMALL EQUIPMENT(S) (MAX 20.000 EUROS). SPECIFY:				
D) TRAVEL EXPENSES (MEETINGS, COURSES, ETC.	400			400
E) PUBLICATION COSTS. SPECIFY:				
F) OVERHEAD (MAX 10%)	900			900
TOTAL COSTS	10.400			10.400

2° ADDITIONAL UNIT(S) WITHIN REGIONE TOSCANA ASL Carrara

	Year 1	Year 2	Year 3	Total
A) NON-STAFF PERSONNEL (CONTRACTS, FELLOWSHIPS, ETC). SPECIFY: ORGANIZATION, SELECTION OF WOMEN, ENROLLING WOMEN	5.500			5.500
B) CONSUMABLES SUPPLIES: STAMPS TO SEND SELF SAMPLING DEVICE, LETTERS, DEPLIANTS, SHIPMENT OF SAMPLES TO ISPO	3.600			3.600
C) SMALL EQUIPMENT(S) (MAX 20.000 EUROS). SPECIFY:				
D) TRAVEL EXPENSES (MEETINGS, COURSES, ETC.)	400			400
E) PUBLICATION COSTS. SPECIFY:				
F) OVERHEAD (MAX 10%)	900			900
TOTAL COSTS	10.400			10.400

16.4 ADDITIONAL UNIT(S) - JUSTIFICATION OF EACH ITEM BUDGET (except for overhead)

a) Non-staff Personnel

ORGANIZATION OF THE STUDY, SELECTION OF WOMEN, ENROLLING WOMEN

b) Consumable supplies

Stamps for Sending SELF SAMPLING KITS DIRECTLY AT HOME OF INVITED WOMEN AND RELATED DOCUMENT

c) Small Equipment(s)

d) Travel Expenses (Meetings, Courses, etc.)

Participation in a scientific meeting and internal meeting

e) Publication Costs

16.5 TOTAL

TOTAL COSTS	Year 1	Year 2	Year 3	Total
	85.000	59.000		144.000