INTRODUCTION

In 2012, cervical cancer was ranked the fourth in incidence and mortality among female cancers worldwide. Globally, cervical cancer had an estimated 528,000 new cases and was responsible for 266,000 deaths in 2012 [1]. Recently, the decreased incidence and mortality rates in developed countries have been attributed to the effectiveness of the screening test for cervical cancer. However, the incidence rate remains high in developing countries, where it accounts for 85% of all cervical cancer cases [2].

According to the Korea Central Cancer Registry data, there were 224,177 new cases of cancer in Korea in the year 2012. After excluding carcinoma in situ cases, cervical cancer was diagnosed in 3,584 cases, which comprised 1.7% of total cancer incidence, and ranking cervical cancer as the seventh most common cancer among females [3].

Although the incidence rate of cervical cancer shows a gradually decreasing trend, the incidence increased from 1993 through 2002 in women in their 20s and in those who were 70 years or older. As the incidence of cervical cancer decreased, an increase in the incidence of cervical cancer with carcinoma in situ was observed in all ages (20-60 years) [4]. This is due to early diagnosis and treatment at a precancerous stage rather than a decrease in de facto incidence of cervical cancer [2,5].

The most important risk factor for cervical cancer is the persistent high-risk human papillomavirus (HPV) infection. The rate of chronic HPV infection is approximately 10%–20% in countries with a high occurrence of cervical cancer and approximately 5%–10% in countries with the low occurrence of cervical cancer. In Korea, the infection rate is reported to be approximately 10%–15%, although different results have been reported [7,10].

The test for HPV, which is a recognized cause of cervical cancer, has been recently included in the screening for cervical cancer. Addition ally, the bivalent and quadrivalent HPV vaccines are being administered clinically. With effective treatments like surgery or concurrent chemoradiation therapy (CCRT), the cure rate of cervical cancer is up to 80%–90% in the early stages (stages I–II), and 60% in stage III. However, the prognosis is still poor with cancer progression to an advanced stage or recurrence.

The present guidelines are based on “The Practice Guidelines for Gynecological Cancers V2” (2010) and recent changes have been added. Key questions from clinical situations were put to thorough discussion with experts in such diverse fields as oncology, pathology, radiation oncology, radiology, and nuclear medicine. We also added an appendix with the evidence tables and the levels of evidence/recommendation.

The present practice guidelines for cervical cancer used the pathological classification (Table 1, modified World Health Organization [WHO] classification) recommended by the Gynecological Pathology Study Group of the Korean Society of Pathologist (GFSkSP). There are 2 classification systems available for cervical cancer staging, the tumor, node, and metastasis (TNM) and International Federation of Gynecology and Obstetrics (FIGO) classification systems. The guidelines that used the FIGO staging were revised in early 2009 (Table 2).

The objective of these practice guidelines is to establish standard policies on issues in clinical practice related to the management in cervical cancer based on the results in published
for hospitalized patients with T2D with mild to moderate glycaemic control treated without injectable therapies at home. Mounting evidence from randomized controlled trials and this real-world study indicate the efficacy and safety of different DPP-4i in the management of hospitalized patients with T2D.

**Author Contributions:** L.M.-P.B., conceptualization, methodology, formal analysis, data curation, writing—original draft preparation, writing—review & editing, supervision; J.J.-G., conceptualization, methodology, writing—review & editing, supervision; N.M.-G., M.D.L.-C., R.G.-M. and F.C.-C., formal analysis, data curation, writing—original draft preparation, writing—review & editing; E.J.F.-G., M.J.-N., M.R.B.-L. and R.G.-H., writing—original draft preparation, writing—review & editing, supervision. All authors approved the final version of the paper.

**Funding:** This work was funded by grants from Internal Medicine Department, cofounded by the Fondo Europeo de Desarrollo Regional-FEDER ("Centros de Investigación en Red" (CIBER, CB06/03/0018) and the Spanish Society of Cardiology (Proyectos de Investigación en Servicios de Salud de Cardiología de la Sociedad Española de Cardiología).

**Acknowledgments:** We thank Claire Conrad for her help with the final English-language version.

**Conflicts of Interest:** R.G.-H. has received consulting fees and honoraria for membership of advisory boards from Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Sanofi and Janssen. None of these financial contributions are related to the manuscript. No other potential conflicts of interest relevant to this article were reported.

**References**

multivariable analysis of the factors involved in test failure is consistent with the literature and so is a strong indicator of the validity of our results. While we demonstrated that heparin could not be held solely responsible for non-reportable results in those patients, we were not able to assess the impact of other treatments on cDNA testing. It is theoretically possible that other treatment commonly used in patients with autoimmune disorders (such as steroids for example) negatively impacted cDNA testing as well. Hui et al. reported increased fetal fraction in a patient with a history of severe autoimmune thrombocytopenia following the introduction of an immunosuppressive treatment by steroids [31]. Such reports raise the question of the impact of treatment on cDNA testing and further studies should focus on understanding this complex relationship.

Conclusion

Our study ruled out the hypothesis that heparin treatment has an impact on cDNA screening and found that autoimmune diseases are associated with test failure. A limitation of our work lies within its retrospective nature and further studies with larger samples and prospective design should help improve our knowledge of the factors involved in non-reportable test result.

Authors' contributions

Conceptualization: YD, AL. Validation: JMC, AL. Formal analysis: JU. All investigation: SG, AJ, PI, LL. Data curation: PI, LL. Original draft: YD, SG, AL. Review, all authors. Visualization: JMC. Supervision: AB, IMC. All authors revised the manuscript for important intellectual content. All authors reviewed and agree to be accountable for all aspects of the work. All authors read and approved the final manuscript.

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Acknowledgements

We sincerely thank D. Marsh for his advice on language editing.

Competing interests

JMC, PI, and LL are employees of Laboratoire CEREA, in which they have a financial interest.

Availability of data and materials

Not applicable.

Consent for publication

Not applicable.

Ethics approval and consent to participate

In line with French regulations requiring prenatal diagnosis, written informed consent was obtained from all patients as the result was used for clinical management. Laboratoire CEREA is authorized by the Regional Health Agency to perform these screening tests. Regarding patients who participated in the DEPOSA study, our local Institutional review board approved this study (CPP Ile-de-France 14-044) (Clinical trial.gov number: NCT0244474).

Funding

None.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 17 September 2018 Revised: 20 November 2018

Published online 03 December 2018

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Specific topics within the context of implementation include which reimbursement and incentive structures work best to facilitate implementation, what training methods are most successful in creating effective multidisciplinary teams, and how can organizational culture shift to support innovation.

Conclusion
The policies and processes for addressing polypharmacy vary widely in the EU, and many countries in the EU are not formally addressing polypharmacy management. These case studies provide examples of initiatives that can be used by countries in the process of developing new polypharmacy management activities, as well as to those looking to scale up existing programs, and highlight the importance of change management and theory-based implementation strategies [30].

Supporting information
S1 File. Data collection tools.

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We would like to thank those who generously participated in the interviews and focus groups for sharing their time and expertise. We would also like to thank the following members of the SIMPATHY consortium for their contributions: Mauro Cataldi, Federico II University Hospital (writing—review & editing related to the Campania Case Study); Antonio Cittadini, Federico II University Hospital, Naples, Italy (formal analysis, writing—review & editing related to the Italian Case Study); Isabel V. Figueiredo, University of Coimbra, Coimbra, Portugal (resources, project administration, methodology); Astrid Forsström, Uppsala University Hospital, Uppsala, Sweden (resources, supervision and writing—review & editing related to the Swedish Case Study); Mary Gittoma, University of Peloponnesus, Korinthos, Greece (conceptualization, funding acquisition, supervision and writing—review & editing related to the Greek Case Study); Simon Harding, Scottish Government, Edinburgh, Scotland (conceptualization, funding acquisition, supervision and writing—review & editing related to the Scottish Case Study); Moira Kinneir, Scottish Government, Edinburgh, Scotland (conceptualization, funding acquisition, supervision and writing—review & editing related to the Scottish Case Study); Nils Michad, Scottish Government, Edinburgh, Scotland (conceptualization and funding acquisition); Michael Scott, Regional Medicines Optimisation Innovation Centre (MOIC) Northern Health and Social Care Trust, Antrim, Northern Ireland (conceptualization, funding acquisition, supervision); Neil Stewart, Kite Innovations Europe, Huddersfield, UK (funding acquisition, project supervision); Theodore Vondetsianos, eHealth Innovation Unit, 1st Regional Health Authority of Attica, Athens, Greece (resources, supervision, writing—review & editing related to the Greek case study), Martin Wilson, Scottish Government, Edinburgh, Scotland (conceptualization, funding acquisition and supervision and writing—review & editing related to the Scottish Case Study).

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Funding acquisition: Albert Alonso, Alpana Mair, Cathy Harrison, Maddalena Illario, Przemyslaw Kadas, Birgit Wiese.


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Supervision: Jennifer McIntosh, Katie MacLure, Derek Stewart, Carles Codina, Fernando Fernandez-Llimos, Ulrika Gillespie, Cathy Harrison, Maddalena Illario, Ulrike Junius-Walker, João Malva, Birgit Wiese.

Writing – original draft: Jennifer McIntosh, Albert Alonso, Katie MacLure, Derek Stewart.


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postmitotic nuclei are located in a central position within the cell (Baluszka et al., 2001). In addition, no mitotic figures have been observed along the root zone; lateral root primordia initiation was observed between 20-25 mm from RCI (Alarcón et al., 2016). In Arabidopsis, the average distance to the earliest mitosis in the pericycle is 3.19 μm and the first mitosis has been observed at 2205 μm from the root tip (Dubrovsky et al., 2001). In maize root, only at 20-30 mm from RCI, some pericycle opposite xylem cells showed condense cytoplasm, indicating they are re-entering the cell cycle (Alarcón et al., 2016). These differences might be caused by the greater elongation root rate in maize which grows 80-90 mm/day, whereas Arabidopsis elongates only 10 mm/day (Dubrovsky et al., 2001).

It has been shown using a tissue-specific quantitative microscopic analysis that some cells of cortex and epidermis were in the first endoderm (DNA contents between 4C and 8C) at their start of elongation. Moreover, nuclei of metaxylem elements in the transition zone accomplished one or two endodermies reaching 32C at their onset of rapid elongation (Baluszka, 1987, 1990; Baluszka and Kubica, 1984; Baluszka et al., 1995). Recently, endoreduplication has been described to occur in plants before cells initiate differentiation (De Veylder et al., 2007). However, we did not observe a relevant number of nuclei with plenary level higher than 4n. Moreover, if endoreduplication was a common process in maize root tip, we would expect hyperplasty to increase as we analysed zones further away from RCI. However, hyperplasty only did not increase in zones elongation zones, but decreased (Table 1).

It has been reported that pericycle cells remain in G1-phase until they re-enter the cell cycle (Vanneste et al., 2007). However, pericycle cells represent just a small fraction of the total amount of cells that form the root tip: epidermal and cortex cells being the most abundant types of cell in root apex. Then, if about 70% of total cells abandon meristem in G2-phase, most of the epidermal and cortex cells must be in G2 when they leave the meristem. It is assumed that epidermal and cortex cell elongation control root longitudinal growth (Alarcón et al., 2014b). Therefore, cells involved in the differentiation process that results in root elongation should be in G2 phase.

Effect of temperature on cell cycle

In our experimental conditions, optimal temperature for maize root elongation was estimated in 30°C, and root elongation decreased by 50% when roots were grown at 20°C. The difference in the several cell cycle phases between roots elongated at 30 and 20°C is presented in Table 1.

The most relevant result was that the percentage of cells in G0/G1 at 20°C diminished by 50% compared to roots grown at 30°C in EZ and DZ. The peak corresponding to G0/G1 phases practically disappeared in flow cytometry profiles at 20°C from the segment located in EZ (3 mm away from RCI). This indicates that cells leaving meristem in G0/G1- or S-phases continue to cycle until they reach G2-phase, where they stop. In addition, we observed that these changes in transition zone are quicker at 30°C. The changes in percentage in G0/G1 reached a stable value that did not change along the TZ, but this fact occurred in EZ when roots were grown at 20°C. In the same way, the strongest changes in S- and G2/M-phases at 30°C occurred in EZ, but they took place in the zone EZ at 20°C. It is well known that cell cycle time increased at suboptimal temperatures (Giménez-Martin et al., 1977). Therefore, cells at 30°C presented a shorter cell cycle time, as they go through the cell cycle phases more rapidly.

In summary, data reported in this work indicate that cells controlling root elongation in maize abandon meristem in G2-phase. When cells leave meristem in G1- or S-phases, they continue the cycle until they reach G2-phase, and then they stop.

These results reveal the role of cell cycle on the balance between the cell proliferation and differentiation processes which occur in the meristem and the elongation zone of the root.

MATERIAL AND METHODS

Plant material and growth conditions

Seeds of Zea mays L. cv DK 826 were washed three times and soaked in distilled water with aeration at 30°C. After 24 h, the seedlings with radicles of about 1 mm length, were placed in plastic boxes on filter paper moistened with distilled water. Seed were also covered with filter paper and grown in darkness. They were kept vertically for 24 h until the roots reached a length of 36-5 mm. Disks with 10 selected seedlings of uniform root length were placed in bottles containing 1,5 l of growth medium composed of a solution of 1 mM HEPES (2-hydroxyethyl)piperazine-2-ethanesulfonic acid) CaCl2, 1 mM and KC1, 10 mM buffered growth solution, and grown at 35°C in darkness. The growth medium was aerated by an aquarium pump. After an acclimation period of 24 h, primary roots were 70-80 mm long and then roots were grown at 30°C or 20°C. Roots elongated 84.75±4.53 and 42.87±2.40 mm/day (mean±sd) at 30°C and 20°C, respectively. The next day, roots of 70-80 mm reached 159-180 mm (30°C) or 115-120 mm (20°C).

Flow cytometry estimation of cell cycle phase progression

Primary roots grown at 30 and 20°C were dissected in several segments according to the different root zones of the root. The root cap was eliminated by removing most apical 5 mm and the following segments were cut 0-1.5, 1.5-3, 3-6, 6-12 and 12-20 mm, and kept in different tubes. The segment was chopped with a razor blade for 30-60 s in a watch glass containing around 2 ml of extraction buffer (Tris-HCL 0.2 M, MgCl2-6H2O 4 mM, EDTA-Na2-2H2O 2 mM, NaCl 85 mM, Metabisulfite 10 mM, 1% PVP 10%, 1% (w/v) Triton X-100 pH 7.5). The resulting extract was passed through a 30 μm filter and centrifuged at 1500 rpm, 5 min. Then, 1 ml of staining buffer (50 μl of RNAase 20 mg/ml, 50 μl of Propidium iodine 6.05% and 900 μl of PBS) was added. Samples were incubated at 37°C in the dark for 30 min. Flow cytometry analysis was performed using a FAC500 flow cytometer (Beckman Coulter, Hialeah, FL, USA). At least 10,000 single nuclei (discarding doublets and aggregates) were acquired in each sample. Experiments were performed in triplicate.

Acknowledgments

We thank Alberto Alvarez-Almanza and Pilar Tomavo from the START at the University of Extremadura for their assistance in performing flow cytometry procedures. We also thank Jose Luis Ruiz for the critical reading of the manuscript and Alberto Salgueiro for reviewing our text in English.

Competing interests

The authors declare no competing or financial interests.

Author contributions


Funding

This work was supported by Conselleria de Estudia y Enseñanza, Junta de Extremadura (research groups OR15112 and OR15158, projects CICESAgrones and BIB1116) and European Regional Development Fund.

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Acknowledgements
This work was supported by the Spanish Ministry of Science and Innovation (grant number BFU2011-23049, co-funded by the European Regional Development Fund; Subprograma Ayudas FPI-MICINN, BES-2012-052293), the Medical Research Council (grant number MR/P006297/1), the Valencia Regional Government (ACOMP2010/199 and PROMETEO/2011/086), and the University of Sussex internal research development fund. The authors declare no competing financial interests.

We thank Karel Svoboda for sharing designs, advice and equipment, Leopoldo Peteanu for sharing designs, Rasmus Petersen for sharing code for behaviour control and for comments on an earlier version of the manuscript, and Elena Giusto for technical help and for the drawings in Figure 1.

Additional information

Funding

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The funders had no role in study design, data collection and interpretation, or the decision to submit the work for publication.

Author contributions

MRB, Conceptualization, Data curation, Software, Formal analysis, Validation, Investigation, Visualization, Methodology, Writing—original draft, Writing—review and editing; MB, Software, Formal analysis, Investigation, Methodology, Writing—review and editing; AP, LB, Investigation, Methodology, Writing—review and editing; LR, STA, CDS, Investigation, Writing—review and editing; MM, Conceptualization, Formal analysis, Supervision, Funding acquisition, Validation, Investigation, Writing—original draft, Project administration, Writing—review and editing.

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Ethics

Human subjects: Human experiments were conducted and underwent ethical review at the University of Sussex. Experiments were approved through the review process in the School of Life Sciences and were given approval identifiers ER/LK250/1, ER/CS502/1, ER/SA533/2. All participants gave informed consent. Participants were provided with an information sheet stating the possibility that the research could be published.

Animal experimentation: All procedures were carried out in accordance with institutional, national (Spain and United Kingdom) and international (European Union directive 2010/63/EU) regulations for the care and use of animals in research. All procedures received prior approval by the relevant institutional ethical committee (Instituto de Neurociencias, CSIC; University of Sussex AWERB) and were covered by the appropriate personal and project licences.
of MIF KD on mitochondrial division and mitochondrial Drp1 oligomer density. Fig. S5 shows that a second splice variant of Drp1 displays independent puncta, but that MIFKD1 does not. Video 1 shows two independent Drp1 punctae stably associated with ER (one goes out of the focal plane briefly). Videos 2 and 3 show Drp1 punctae translocating to mitochondria (Video 2 does not have an ER marker; Video 3 has an ER marker). Videos 4 and 5 show Drp1 punctae translocating to mitochondria, followed by mitochondrial division (Arylsyan). Video 9 shows colocalization of GFP, Drp1, and mStrawberry-MIF on ER. Videos 9 and 10 show the change in independent Drp1 punctae after mStrawberry treatment. In Video 9, the punctae increase, but in Video 10 (preincubated with latrunculin A) the punctae do not increase.

Acknowledgments

We thank Mike Ryan for GFP; l. Apany Seguro for advice on organellar fractionation, Heidi McBride for FDC-deficient cells, Maya Schuldiner for discussions on Traf2 protein, Anna Hatch for editing, and Peter Rocs for being receptive to anything.

Support was provided by the National Institutes of Health GM069918, GM 106009, and P20 GM113122 to H.N. Higgins, National Institutes of Health NS565244 and NS 097908 to S. Strack, and National Institutes of Health S1000D010330 to the Norris Cotton Cancer Center.

The authors declare no competing financial interests.

Author contributions: W.K.J.: conceptualization, methodology, investigation, formal analysis, writing, R. Chakraborti: conceptualization, methodology, investigation, formal analysis. X. Fan and I. Schonfeld: methodology, investigation, formal analysis. S. Strack: methodology, investigation, H.N. Higgins: conceptualization, project administration, writing, funding acquisition.

Submitted: 17 October 2016
Revised: 1 June 2017
Accepted: 18 September 2017

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