6 Castle PE, Stoler MH, Wright TC Jr, Sharma A, Wright TL, Behrens CM. Performance of carcinogenic human papillomavirus (HPV) testing and HPV16 or HPV18 genotyping for cervical cancer screening of women aged 25 years and older: a subanalysis of the ATHENA study. *Lancet Oncol* 2011; **12:** 880–90.

7 Carozzi F, Confortini M, Dalla PP, et al. Use of p16-INK4A overexpression to increase the specificity of human papillomavirus testing: a nested substudy of the NTCC randomised controlled trial. *Lancet Oncol* 2008; **9:** 937–45.

8 Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *CA Cancer J Clin* 2012; **62:** 147–72.

9 Wentzensen N, Schwartz L, Zuna RE, et al. Performance of p16/Ki-67 immunostaining to detect cervical cancer precursors in a colposcopy referral population. *Clin Cancer Res* 2012; **18:** 4154–62.

International Rare Cancers Initiative

The definition of a rare cancer has not been agreed internationally. In Europe, rare diseases are often defined as those with a prevalence of less than 50 per 100 000.[1] In the USA, a published definition of a rare cancer is less than 15 per 100 000 per year.[2] The estimated yearly incidence of all rare cancers in Europe, (based on the RARECARE definition of an incidence of <six per 100 000 per year)[3] is about 108 per 100 000, corresponding to 541 000 new diagnoses every year or 22% of all cancer diagnoses, including all cancers in children. This incidence is more than any single common cancer. About 4 300 000 patients are living in the European Union with a diagnosis of a rare cancer—24% of the total cancer prevalence. However, as a result of the low incidence of individual rare cancers, such malignancies are difficult to study.

Patients with rare cancers face particular challenges, including late or incorrect diagnosis, difficulties accessing clinical expertise and appropriate treatments, possible lack of interest in developing new therapies, high uncertainty in clinical decision making, and the scarcity of available registries and tissue banks. Furthermore, investigators face difficulties in undertaking clinical studies because of the small number of patients. Unfortunately, the average outcome for patients with a rare cancer is therefore worse than that of patients with more common cancers.[3] For rare cancers, international collaboration is essential to run clinical trials of adequate statistical power to answer important questions in a reasonable timeframe. These trials can accrue faster, and they often lower collective administrative costs by sharing infrastructure and centralised resources. However, investigators who undertake clinical trials of treatments for rare cancers face a number of unique challenges, including discrepancies in regulatory requirements, intellectual property concerns, restrictive contractual agreements, and the coordination of operations between organisations. These challenges might be overcome through careful planning, frequent communication, and cooperative collaboration.[4]

International trials in rare diseases are practicable with appropriate funding, planning, and support; in an attempt to encourage the development of international trials for rare cancers, the International Rare Cancers Initiative (IRCI) was established early in 2011. IRCI is a joint initiative between the National Institute for Health Research Cancer Research Network, Cancer Research UK, the National Cancer Institute, and the European Organisation for Research and Treatment of Cancer (EORTC). The objective of this initiative is to facilitate the development of international clinical trials for patients with rare cancers to boost the progress of new treatments for these patients. For the purpose of this initiative, rare has been broadly defined as an incidence of less than two per 100 000. Occasionally, rare clinical scenarios have also been considered. So far, IRCI has excluded rare molecular subtypes of common cancers. However, a rare molecular subtype could be considered if it is a distinct, prospectively identifiable rare subgroup with a strong rationale for separate research, rather than inclusion as a molecular stratum in a mainline trial. Priority has been given to cancers with potential for an interventional trial (usually randomised) rather than an audit, registry, or non-trial tissue collection. The IRCI hopes to encourage the use of innovative trial designs to maximise the potential for research questions to be answered, and to identify and overcome barriers to international trials to allow agreed IRCI trials to run smoothly.

At the outset of the initiative, clinical communities associated with each partner organisation were asked to identify rare cancers when there was enthusiasm for international collaborations and the potential

for development of an interventional clinical trial. Nine rare cancers have formed the core activities of IRCI so far: salivary gland cancer, anaplastic thyroid cancer, small bowel adenocarcinoma, gynaecological sarcoma, fibrolamellar hepatocellular carcinoma, penile cancer, thymoma, ocular melanoma, and relapsed or metastatic anal cancer. Of the nine groups investigating these cancers, seven are actively developing ten clinical trials for submission to appropriate funding bodies. The IRCI Gynaecological Sarcoma Group has made great progress, and the first IRCI study opened to recruitment: a phase 3 randomised trial of gemcitabine plus docetaxel followed by doxorubicin versus observation for uterus-limited, high-grade uterine leiomyosarcoma (IRCI 001; ClinicalTrials.gov registration number NCT01533207). The study opened to recruitment at the Memorial Sloan Kettering Cancer Center (New York, USA) early in September, 2012. The study is being processed by the EORTC and Glasgow Clinical Trials Unit, and is due to open to recruitment in Europe in the next few months.

Although the implementation of international clinical trials is difficult and time consuming, it is a worthwhile effort to rapidly complete randomised controlled trials identifying interventions that will improve the outcome for patients with rare cancers.

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1 EC of the European Parliament and of the Council, June 1999. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31999D1295:EN:HTML (accessed November 26, 2012).
2 Greenlee R, Goodman M, Lynch C, Platz C, Havener L, Howe H. The occurrence of rare cancers in US adults, 1995–2004. *Public Health Rep* 2010; **125:** 28–43.
3 Gatta G, van der Zwan JM, Casali PG, et al, for the RARECARE working group. Rare cancers are not so rare: the rare cancer burden in Europe. *Eur J Cancer* 2011; **47:** 2493–511.
4 Tan SB, Dear KB, Bruzzi P, Machin D. Strategy for randomised clinical trials in rare cancers. *BMJ* 2003; **327:** 47–49.