and colleagues[3] identified the IELSG32 study[8] as the only other randomised trial investigating rituximab in primary CNS lymphoma. In IELSG32,[8] the HR for progression-free survival was 0·52 (95% CI 0·32–0·86) and for overall survival was 0·63 (0·42–1·02), both strongly in favour of rituximab.

Although the HOVON 105/ALLG NHL 24 trial did not meet its primary endpoint, to conclude from this single study that rituximab is not active in primary CNS lymphoma neglects the total body of clinical evidence. Considering the established benefit for rituximab in systemic diffuse large B-cell lymphoma[1] and results from both randomised trials[3,8] in primary CNS lymphoma, we believe rituximab should remain an indispensable component in the treatment of patients with primary CNS lymphoma, irrespective of age.

*Benjamin Kasenda, *Gerald Illerhaus*
Department of Haematology/Oncology and Palliative Care, Klinikum Stuttgart, Stuttgart Cancer Centre, 70174 Stuttgart, Germany (BK, GI); and Department of Medical Oncology, University Hospital Basel, Basel, Switzerland (BK)
g.illerhaus@klinikum-stuttgart.de

We declare no competing interests.

1 Rancea M, Will A, Borchmann P, Monsef I, Engert A, Skoetz N. Fifteenth biannual report of the Cochrane Haematological Malignancies Group—focus on non-Hodgkin's lymphoma. *J Natl Cancer Inst* 2013; **105:** 1159–70.
2 WHO. WHO classification of tumours of haematopoietic and lymphoid tissue, 4th edn. Geneva: World Health Organization, 2008.
3 Bromberg JEC, Issa S, Bakunika K, et al. Rituximab in patients with primary CNS lymphoma (HOVON 105/ALLG NHL 24): a randomised, open-label, phase 3 intergroup study. *Lancet Oncol* 2018; published online Jan 7. http://dx.doi.org/10.1016/S1470-2045(18)30747-2.
4 Villano JL, Koshy M, Shaikh H, Dolecek TA, McCarthy BJ. Age, gender, and racial differences in incidence and survival in primary CNS lymphoma. *Br J Cancer* 2011; **105:** 1414–18.
5 Ferreri AJM, Cwynarski K, Pulczynski E, et al. Whole-brain radiotherapy or autologous stem-cell transplantation as consolidation strategies after high-dose methotrexate-based chemoimmunotherapy in patients with primary CNS lymphoma: results of the second randomisation of the International Extranodal Lymphoma Study Group-32 phase 2 trial. *Lancet Haematol* 2017; **4:** e510–23.
6 Illerhaus G, Kasenda B, Ihorst G, et al. High-dose chemotherapy with autologous haemopoietic stem cell transplantation for newly diagnosed primary CNS lymphoma: a prospective, single-arm, phase 2 trial. *Lancet Haematol* 2016; **3:** e388–97.
7 Omuro A, Correa DD, DeAngelis LM, et al. R-MPV followed by high-dose chemotherapy with TBC and autologous stem-cell transplant for newly diagnosed primary CNS lymphoma. *Blood* 2015; **125:** 1403–10.
8 Ferreri AJ, Cwynarski K, Pulczynski E, et al. Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial. *Lancet Haematol* 2016; **3:** e217–27.

Self-collected versus clinician-collected samples for HPV testing


Voisin/Phanie/Science Photo Library

Published Online January 15, 2019 http://dx.doi.org/10.1016/S1470-2045(18)30934-3
See Articles page 229

In *The Lancet Oncology*, Nicole Polman and colleagues[1] report the results of a randomised trial, nested in the Dutch cervical screening programme, in which clinical performance of human papillomavirus (HPV) testing was compared between self-collected and clinician-collected samples. Encouragingly, testing done on self-samples was non-inferior to that done on clinician-collected samples in terms of detection of cervical intraepithelial neoplasia grade 2 or worse (CIN2+; relative sensitivity 0·96 [95% CI 0·90–1·03]; relative specificity 1·00 [0·99–1·01]) and cervical intraepithelial neoplasia grade 3 or worse (CIN3+; relative sensitivity 0·99 [0·91–1·08]; relative specificity 1·00 [0·99–1·01]).

For the past 50 years, screening for and treatment of precancerous lesions have helped to decrease the incidence of cervical cancer.[2] However, cervical screening has some challenges.

First, cytological assessment of clinician-collected samples has been the backbone of cervical screening, originally in the form of manual assessment of conventional smears and, during the past decade, as liquid-based cytology with computer-assisted reading. The sensitivity of cytology, however, is low, and repeated testing every 3–5 years is needed for effective disease control.[3] In Europe, a woman is typically invited for cervical screening 13–15 times between the ages of 25 years and 64 years,[4] and screening can be a burden, both on women and on health-care resources. HPV testing is now an attractive alternative to cytology because HPV testing of clinician-collected samples has been proven to provide better protection against cervical cancer than does cytological assessment of these samples,[5] and primary HPV screening thus allows for a longer screening interval than does cytological screening.

Second, despite efforts in many countries to organise screening in population-based programmes, attendance rates are rarely more than 75%, and about half of cervical

cancer cases occur in the quarter of women who do not comply with screening. To overcome this challenge, self-collection has been tried as an alternative to clinician-based sampling. Self-collection devices were sent to women in Copenhagen, Denmark, in the 1970s to spare working-class women the need to take time off work for screening.[6] However, self-collection does not provide sufficient cellular material for cytological assessment, and has, therefore, been a dormant technology until the era of HPV testing.

In 2014, a meta-analysis[7] of the published, mainly small, studies showed that HPV testing of self-collected samples had sensitivity for the detection of CIN3+ similar to that of cytological assessment of clinician-collected samples. On the basis of this study, many screening programmes have offered self-collection to women who do not attend regular screening. Typically, about 20–30% of former non-attenders used the self-collection option, and this approach has helped to increase screening coverage.[8,9]

Self-collection might also be a preferable option for regular attenders of screening, but the aforementioned meta-analysis[7] showed that HPV testing had lower sensitivity when done on self-collected samples than on clinician-collected samples. Full conversion of screening programmes to self-collection has, therefore, not been recommended, although this option is attractive in terms of its potential to save women's time and health-care resources.

In the IMPROVE study,[1] Polman and colleagues compared, for the first time, HPV testing on self-collected samples with that on clinician-collected samples in a large trial undertaken within the framework of a routine screening programme. The two sample types had similar sensitivity and specificity for the detection of CIN2+ and for CIN3+. These results are very promising. The IMPROVE study used the Evalyn Brush for self-collection, the Thin Prep PreserveCyt media for suspension of the sample in the laboratory, and the GP5+/6+ PCR enzyme immunoassay for HPV DNA testing. These technical specifications should be taken into account in the interpretation of the results. In the 2014 meta-analysis,[7] no difference was found between sample types in terms of sensitivity for CIN2+ in the few studies that used the GP5+/6+ PCR assay for HPV testing, and the overall reduced sensitivity of the self-collected samples was driven by results from studies that used the Hybrid Capture 2 assay for HPV testing. Further comparisons between outcomes of the GP5+/6+ PCR assay with those of new generation HPV assays are therefore needed before conversion to self-collection can be generally considered in screening programmes.

Only 8·8% of the women invited to the IMPROVE trial participated. This low proportion might reflect reluctance to be included in a randomised trial, but might also reflect reservations against self-collection. Notably, only 20–30% of those offered self-collection in the non-attender trials[8,9] participated. In birth cohorts not yet vaccinated against HPV, high screening coverage is the best tool for cervical cancer control. Although HPV testing of self-collected samples is a promising way forward, both the IMPROVE study and non-attender trials[8,9] indicate that clinician collection is probably not the only obstacle to increasing screening attendance.

Elsebeth Lynge
Nykøbing Falster Hospital, University of Copenhagen, Copenhagen, DK-4800 Nykøbing Falster, Denmark
elsebeth@sund.ku.dk

EL receives HPV test kits from Roche for a screening trial.

1 Polman NJ, Ebisch RMF, Heideman DAM, et al. Performance of human papillomavirus testing on self-collected versus clinician-collected samples for the detection of cervical intraepithelial neoplasia of grade 2 or worse: a randomised, paired screen-positive, non-inferiority trial. *Lancet Oncol* 2019; published online Jan 14. http://dx.doi.org/10.1016/S1470-2045(18)30763-0.
2 Hakama M. Trends in the incidence of cervical cancer in the Nordic countries. In: Magnus K, ed. Trends in cancer incidence: causes and practical implications. Washington: Hemisphere Publishing Corp, 1982: 270–92.
3 IARC Working Group on evaluation of cervical cancer screening programmes. Screening for squamous cervical cancer: duration of low risk after negative results of cervical cytology and its implication for screening policies. *BMJ* 1986; **293:** 659–64.
4 Ponti A, Anttila A, Ronco G, et al. Cancer screening in the Europe Union (2017): report on the implementation of the Council Recommendation on cancer screening. https://ec.europa.eu/health/sites/health/files/major_chronic_diseases/docs/2017_cancerscreening_2ndreportimplementation_en.pdf (accessed Dec 11, 2018).
5 Ronco G, Dillner J, Elfström KM. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of tour European randomised controlled trials. *Lancet* 2014; **383:** 524–32.
6 Lynge E. Vaginal cytological examinations in Denmark. *Ugeskr Laeger* 1982; **144:** 124–29 (in Danish).
7 Arbyn M, Verdoodt F, Snijders PJ, et al. Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: a meta-analysis. *Lancet Oncol* 2014; **15:** 172–83.
8 Gök M, Heideman DA, van Kemenade FJ, et al. Offering self-sampling for human papillomavirus testing to non-attendees of the cervical screening programme: characteristics of the responders. *Eur J Cancer* 2012; **48:** 1799–808.
9 Karjalainen L, Anttila A, Nieminen P, Luostarinen T, Virtanen A. Self-sampling in cervical cancer screening: comparison of a brush-based and a lavage-based cervicovaginal self-sampling device. *BMC Cancer* 2016; **16:** 221.