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Self-sampling to reach non-participating women

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Even the best organised, free of charge, national cervical cancer screening programs only attracts approx. 3 out of 4 invited women for screening. In Denmark, the 25% non-attending women accounts for almost half the cervical cancers diagnosed annually[1]. Reasons for non-attendance varies across the globe, yet universal motives include not liking/embarrassment in connection with the gynaecology examination, issues with access to doctor's appointments, or quite simply that women don't think they need screening for one reason or the other[2]. Self-sampling in the comfort of the woman's own home, in her own good time, and without risk of social, cultural or religious stigmatization offers an opportunity to target one of the largest single challenges of organised cervical cancer screening, the participation rate[1,3,4]. Here, we will summarize some of our experiences and considerations with self-sampling from the Copenhagen Self-sampling Initiative (CSi), inviting almost 24.000 screening non-attenders for self-sampling.[5,6]

Two main strategies have been evaluated: the Opt-out (also called "mail-to all") strategy where identified non-responders are mailed a self-sampling kit directly, or Opt-in where identified non-responders are invited to request a self-sampling kit

Opt-in or Opt-out: That's the question…

How to best recruit non-attenders to screening is the question, and several clinical trails have investigated self-sampling as alternative to clinical taken samples. Two main strategies have been evaluated, the Opt-out (also called "mail-to all") strategy where identified non-responders are mailed a self-sampling kit directly, or Opt-in where identified non-responders are invited to request a self-sampling kit. The former strategy has the advantage of presenting the self-sampling kit to all non-responders in the hope that more will accept and return a sample for analysis, but the disadvantage is a high loss of unused kits never returned for analysis. In other word, you may recruit more non-responders but it comes at a (costly) premium. The Opt-in strategy has the advantage of lower costs by only shipping the kits to women who after invitation actively request the kit. The disadvantage is that non-responders will have to go through the additional step of actively ordering the self-sampling kit which may lead to a lower participation.[2] Table 1 shows key features from a selection of HPV self-sampling studies.

In terms of participation, the studies vary widely. From 6.4% (Szarewski et al, UK, Opt-out) to 39% (Sanner et al, Sweden, Opt-in), reflecting the design of the self-sampling approach, the population targeted, when and where.[2] At

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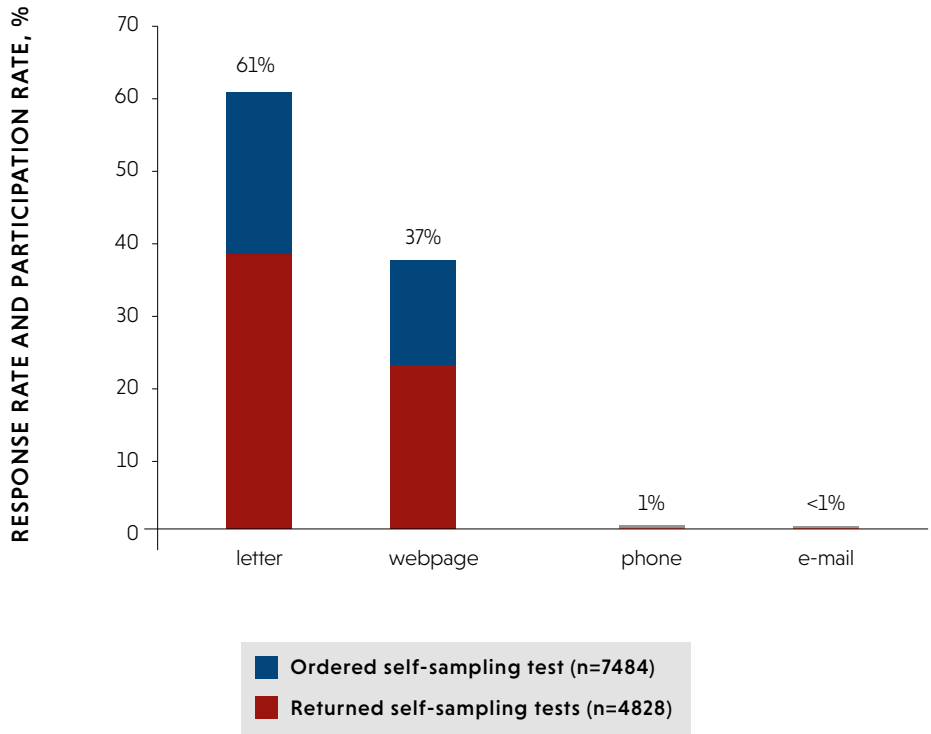
Table 1

Summary of studies assessing different invitation strategies for self-sampling

Invitation strategy	Country & Study design	Study size	Target age (years)	Participation Rate	Reference
Opt-in	Denmark Cross sectional	N=4874	27-64	**20%** by self-sampling+ **10%** by clinician taken samples after invitation	Lam J.U.H. et al., Int J Cancer 2017
	Sweden Cross sectional	N=369	35-50	**32.0%**	Stenvall H. et al., Acta Derm Venereol 2007
	Sweden Cross sectional	N=3000	30-58	**39.0%**	Sanner K. et al., Br J Cancer 2009
	Sweden RCT	N=800	30-62	**16.0%**	Broberg G. et al., Int J Cancer 2014
Opt-in & opt-out	Italy RCT	Opt-in: N=622 Opt-out: N=622	35-65	Opt-in : **8.7%** Opt-out: **19.6%**	Giorgi Rossi P. et al., Br J Cancer 2011
	Italy RCT	Opt-in: 4513 Opt-out: 4516	30-64	Opt-in: **10.5%** Opt-out: **19.6%**	Giorgi Rossi P. et al., Br J Cancer 2015
Opt-out	Netherlands RCT	N= 2546	30-50	**28.9%**	Bais A.G. et al., Int J Cancer 2007
	UK RCT	N=27,792	30-60	**26.6%**	Gök M. et al., BMJ 2010
	Finland RCT	N=8000	30-65	**39.0%**	Gyllensten U. et al., Br J Cancer 2011
	Sweden RCT	N=1500	NR	**6.4%**	Szarewski A. et al., Br J Cancer 2011
	UK RCT	N=2,397	30-60	**27.7%**	Virtanen A. et al., Cancer Epidemiol Biomarkers Prev 2011
	Finland RCT	N=2000	39-60	**34.0%**	Wikström I. et al., Br J Cancer 2011
	Netherlands RCT	N=26,145	26-63	**30.8%**	Gök M. et al., Int J Cancer 2012
	Sweden RCT	N=1000	32-65	**14.7%**	Darlin L. et al., J Clin Virol 2013
	France RCT	N=8,829	35-69	**18.4%**	Sancho-Garnier H. et al., Int J Cancer 2013
	UK RCT	N=3,000	25-65	**13.0%**	Cadman L. et al., J Med Screen 2014

Figure 1

Response and participation rate by letter, webpage, phone and email



current it is not possible to point to Opt-in or Opt-out as the universally superior option, and HPV self-sampling as a supplement to organised cervical screening should be designed and operationalized with respect to the screening program it is proposed to supplement.[7] In our setting, of 23,632 women invited, 20% returned the self-sample for analysis with 39% of those being long term unscreened (≥10 years unscreened).[5]

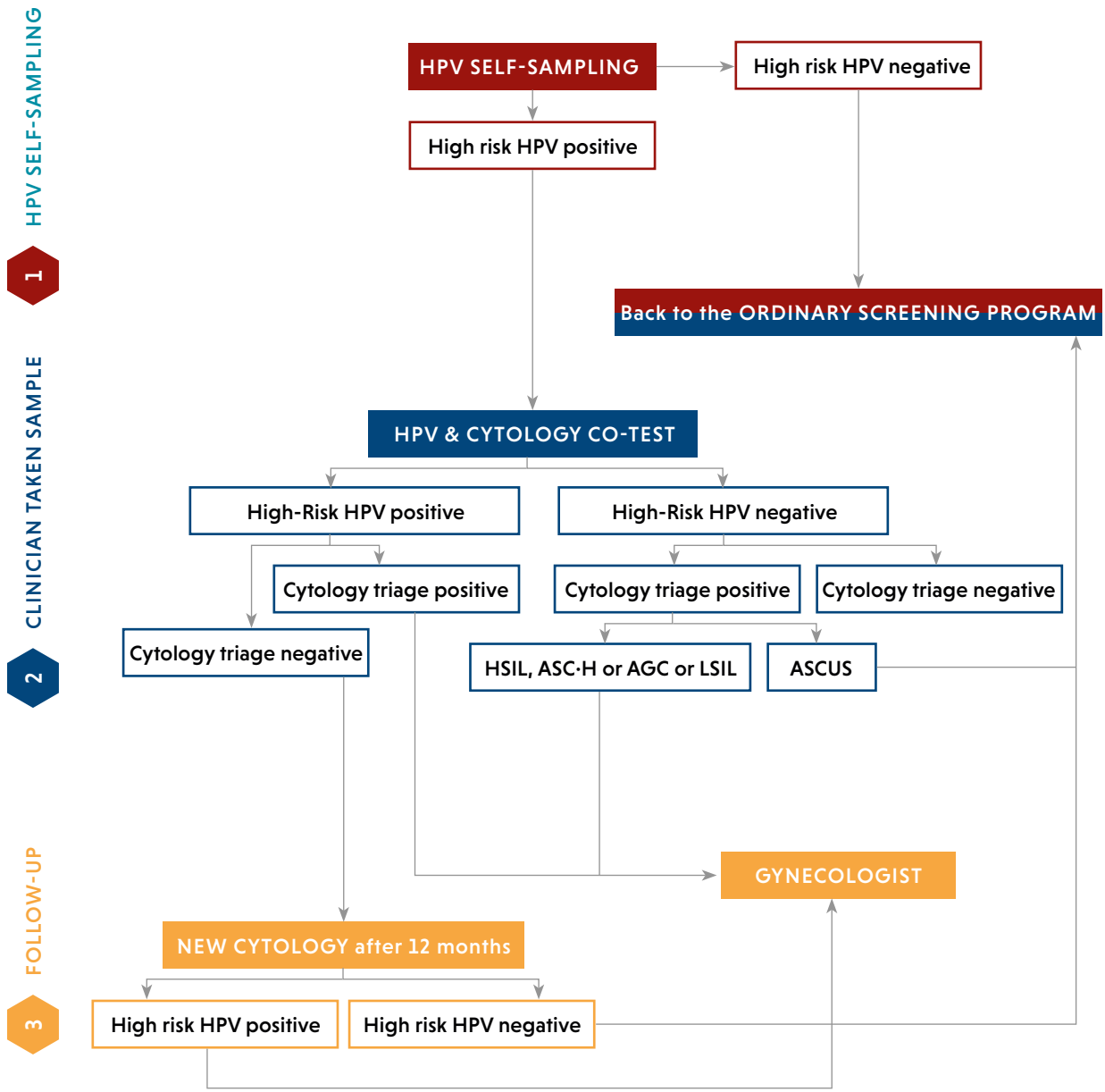
HPV self-sampling to screening non-attenders should not only be evaluated on the number of returned samples, but also include derived screening activity

The effect of HPV self-sampling on screening participation

Most often, studies on HPV self-sampling compare to a group of women offered clinician based sampling are offered clinician based sampling. We however, also focused on the screening participation by clinician taken samples after the non-attenders received the invitation for self-sampling, acknowledging that the total participation rate of a self-sampling initiative will consist of both. In our setting, an additional 10% of the non-attenders invited for self-sampling chose to have a clinician taken sample.[3] Overall, this resulted in 30% participation rate.

Figure 2

Proposed follow-up strategy for HPV positive women by self-sampling



The point is, that introducing HPV self-sampling as an alternative to screening non-attenders should be evaluated not only on the directly measurable effect in term of returned brushes for analysis. The derived "motivational effect" for screening participation may be substantial amongst non-attenders. Passive register follow-up in 2017 of the women invited for CSi showed that 2 year after the invitations for self-sampling, 18.2% of the invited women had a regular, clinician taken sample registered.[6] This is an increase from the 10% in the implementation period.[5] Without arguing this as a direct effect of the self-sampling invitations, at least it indicates that a large proportion of screening non-attenders are susceptible to accept screening. In retrospect, it may not be surprising that women presented with options for screening with screenings options actively choses between those options.

The power of communication

"The single biggest problem in communication is the illusion that it has taken place" wrote George Berhard Shaw. Communication strategies are pivotal to informing women about screening and why it is important to participate. One of the key design items we focused on in CSi was to provide relevant information and facilitate easy access to "Opt-in" by offering a web-based response platform. The special designed web-page system with App like features included a re-directing QR code on the invitation letter for smart phone, tablets or computer use knowing that 95-98% of all Danish women have access to a smart phone or similar devices. Moreover we focused on offering language options other than Danish on the web-platform, thereby attempting to bridge any linguistic divides. Looking at all responders, almost 40% used the electronic platform for opting in[5] (Figure 1), underlining that offering easy ways to accept the invitation is beneficiary for accruing participation. The effect of multi-language information is yet to be reported, but almost 30% of those accepting self-sampling were of non-danish origin[7], which is double up compared to the proportion of non-Danes in the general population.

HPV self-sampling is a viable supplement to recruit screening non-responders

From an operationalization point-of-view these are interesting points. Firstly, communication through web and app based platforms holds a huge potential to improve the user experience compared to letter based correspondence, but it also confers large cost savings on postage for the program. Secondly, language versions of invitation and web based contents require a small effort for a potentially great gain in participation. We are currently exploring these items in more detail in the coming three years, 2017-2019, as self-sampling is rolled out as a supplementary offer to screening non-attenders in our program.

Bringing HPV self-sampling into the organised screening program

HPV self-sampling to increase screening participation is becoming an essential supplement to organised screening. Yet, a number of key features still needs to be addressed to ensure optimal performance of self-sampling in organised screening programs. Firstly, how to follow-up HPV positive women by self-sampling? Here we propose a conservative strategy (Figure 2) referring HPV positive women for a clinician taken sample for cytology and HPV co-testing. Based upon this follow up sample, the woman can be referred in concordance with standard-of-care practice, national recommendations or guidelines, in effect shuttling her into the organised screening

program. Loss to follow up after self-sampling has been voiced as a concern, but in CSi, 87% (N=639) of the self-sampling positive women went for follow-up.[6] This resulted in an initial detection of 101 ≥CIN2 cases with more to come as follow up becomes more complete over time.[6] But does the follow-up necessarily have to be by regular, clinician taken sample? Or could a subset of women benefit from being referred directly for colposcopy saving them at least one gynaecological examination? This is still an open question that should be addressed weighting the balance between the absolute minimum required versus too many examinations, knowing that the examinations are often the barrier to screening.

Risk-based triage strategies using genotype information or methylation markers could potentially come in play, given that both types of analysis can be conducted directly on the original self-sample. Finally, routine self-sampling emphasises the need for HPV assay validation criteria on self-samples. However, no joint international recommendations or requirements have been established to this end.

In conclusion, HPV self-sampling is a viable supplement to recruit screening non-attenders. How and in which way HPV self-sampling will be part of organised screening programs must be defined locally, in order to get the best synergy effects with the regular screening program. By the end of the day, what matter is getting non-responders screened.

Disclosure of interests:
JB used to serve as a paid advisor to Roche and Genomica, and has received honoraria from Hologic/Gen-Probe, Roche, Qiagen, Genomica, and BD diagnostics for lectures. He is principal investigator on studies funded by BD diagnostics, and Qiagen Ltd. DE has no interests to declare. ■

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