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REVIEW ARTICLE

Self-collected Papanicolaou tests in the United States market: more questions than answers

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The United States Food and Drug Administration held a public hearing in January 2018 to consider how it should evaluate a self-collection device for cervical cytology. Although no such device has been approved for use in the US market, the implications for patients and cytologists could be both sweeping and complex. Herein, the existing literature basis for self-collected Papanicolaou testing is reviewed, and some questions raised by this testing are considered. Questions include: what would be the value to patients; how effective could self-collected Papanicolaou tests be; how might ordering and collection work; what are the unique pre-analytic, analytic, and post-analytic challenges of self-collected Papanicolaou testing; and what effect might self-collection have on cervical cancer rates?

Contents

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What if women could collect their own Papanicolaou tests in the comfort of their own home—or at least in a private room in the doctor's office? Would this increase utilization of Papanicolaou tests? Would women find this more or less stressful than provider-collection? Could it be as effective at preventing cancer as the existing Papanicolaou test? Is it even feasible? The authors participated in a public hearing at the US Food and Drug Administration (FDA) in January 2018 that was intended to advise the FDA on what research would be required to demonstrate the safety and efficacy of a self-collection Papanicolaou test device.[1] Although the current state of the literature on Papanicolaou test self-collection is quite limited, there is substantially more evidence of the potential for self-collection for HPV testing. The announcement of an FDA hearing suggests that there is likely to be commercial interest in developing such a system. This possibility raises many questions for cytologists, some of which are discussed in this article (Table 1).

Table 1 Some unanswered (or incompletely answered) questions about self-collected Papanicolaou testing in the United States.

I. What is the value of self-collection?
- Can it reduce the underscreened population?
- Can it improve the experience of women who might switch to it?

II. Is self-collection feasible and effective?
- What would a convincing clinical study of self-collection look like?
- How would self-collected HPV testing interact with self-collected Papanicolaou testing?

III. Is self-collection for cervical cytology achievable and reliable?
- Can cervical pre-cancers be reliably diagnosed without direct sampling of the transformation zone?
- If not, how can self-collection sample the transformation zone?

IV. Would women use it?
- How many underscreened women would use it?
- How many provider-screened women would switch to it?

V. How would self-collection work?
- How are the advantages and disadvantages of self-ordering versus provider-ordering weighed to maximize success?
- How are the advantages and disadvantages of home collection versus clinic collection weighed to maximize success?

VI. How would the testing laboratory be selected?

VII. What are the pre-analytic issues with self-collection?
- Collection issues: does the patient understand and follow the instructions? Is the collection date correct? Is the requisition completed accurately?
- Medium/transport issues: Is the medium safe? Does the medium keep cells intact over a wide variety of conditions, eg, transport temperature and delivery time?

VIII. What are the analytic issues with self-collection?
- Does the collection/transport medium create cellular artifacts that require further study or special training?
- Can HPV testing be performed on the same sample?
- Are collection method-specific adequacy criteria necessary?

IX. What are the post-analytic issues with self-collection?
- What would a Papanicolaou test report designed for the patient look like?
- By what mechanism should results be reported (mail, phone, email, etc)?
- What is the legal responsibility and liability of the laboratory for delivering the report to the patient?
- How does the laboratory refer the patient for follow-up management?

X. How would Papanicolaou self-collection affect cancer rates?
- What, if any, difference in sensitivity would self-collected screening have compared to provider-collected screening?
- How many women overall would switch to the self-collected test? How many who are currently underscreened? How many who are currently adequately provider-screened?
- Would abnormal results delivered directly to patients impact the likelihood of appropriate management?
- How accurately would screening intervals be maintained if cervical cancer screening is separated from scheduled physician visits?

It is important to note at the outset that this discussion relates specifically to the United States. The significance and implications of self-collected cytology (Papanicolaou) testing in the United States, a developed nation with a fairly high baseline rate of medical access in general and cervical cancer screening in particular, are markedly different than in nations with low cervical cancer screening rates resulting in higher death rates, and are also likely to be different in nations with more systematic, rather than opportunistic, approaches to cervical cancer screening.

What is the value of self-collection?

The primary reason cited by enthusiasts for implementing self-collection is to improve screening of women who do not regularly undergo cervical cancer screening through provider-collected Papanicolaou testing. Approximately 83% of women of screening age in the United States report having a Papanicolaou test in the last 3 years.[2] The remainder, approximately 8 million women ages 21 to 65 years, were not screened for cervical cancer in the last 5 years.[3] These women represent the source of more than half of incident cervical cancers in the United States.[4] Research indicates a wide variety of reasons that these women are not enrolled in screening, including but not limited to: lack of easy access to care due to cost, lack of insurance, lack of a primary provider, distance to providers, unpleasant sampling experiences, and cultural reasons.[5] Many of these reasons are potentially ameliorated by self-collection. A recent meta-analysis of *human papillomavirus* (HPV) self-collection identified greater compliance (relative compliance: 2.14; 95% CI: 1.30 to 3.52) on average with self-collection than provider-collection.[6] The impact in less-developed nations with less access to providers and lower baseline rates of cervical cancer screening is potentially even more substantial.

A second reason for pursuing Papanicolaou test self-collection is increased comfort and/or convenience of those who currently receive provider-collected Papanicolaou testing but would prefer a self-collection method. Multiple studies have shown that women prefer self-collection of specimens to physician-collection for HPV testing, finding self-collection more convenient, less uncomfortable, and less embarrassing than provider-collection, and indicating a significant preference for self-collection.[6-9] Of particular concern is that certain subgroups of the population have less frequent screening rates than the general population; these disparities are related to socioeconomic class, geographic region, race,[10] and obesity.[11]

Is self-collection feasible and effective?

The current state of the scientific literature on self-collection for cytology is very limited. The concept of self-collected Papanicolaou testing, however, is almost as old as the Papanicolaou test itself. Papanicolaou himself published one of the earliest studies of self-collected Papanicolaou tests,[12] using a tampon-type device designed by Draghi.[13] Of women who were diagnosed with cancer, only 3% were called benign by this method, although in another 17% the diagnosis was deferred due to scant cellularity or poor quality. Bader et al found a 97% rate of agreement between self-collected specimens using the Draghi device and physician-collected samples in a relatively unselected population of 2694 women.[14] They reported plans to test this device in a true screening situation, but the results do not appear to have been published. In the 1960s, Davis introduced a lavage device.[15] Some authors found this device comparable to provider-collected Papanicolaou tests,[16-18] but others found it less sensitive.[19,20] A number of more recent studies that directly compared a variety of self-collection devices to the standard provider-collected Papanicolaou test are detailed in Table 2.[21-33] Most studies had a sample size in the hundreds, with the total number of epithelial abnormalities identified from 1 to 364, but with a much smaller number of high-grade squamous intraepithelial lesions or carcinomas. Some were population-based studies and others were enriched with abnormal cases. The devices can be separated into washing-style devices that use fluid to exfoliate cells, and direct brushing-type devices that mechanically exfoliate cells. In general, washing-type devices showed adequacy rates of 86% to 91.5% based on squamous cellularity. Only 1 study commented on the presence of endocervical cells—it found they were present in only 8.6% of self-collected specimens compared with 79.1% of provider-collected Papanicolaou tests.[24] Concordance with the provider-collected Papanicolaou tests varied from 41% to 81%, and in studies with colposcopy and biopsy to confirm the diagnosis, sensitivities were consistently and substantially lower with self-collected Papanicolaou tests than provider-collected Papanicolaou tests. A variety of brushing-type devices have been studied. Adequacy rates for squamous cellularity varied from 95% to 100%. Several studies noted that endocervical cells were present in a much lower proportion of self-collected than provider-collected Papanicolaou tests.[28,30-32] Agreement between self-collection and provider-collection varied from 70% to 100%. In studies that had colposcopy and biopsy as a gold standard, sensitivity of brushing-type self-collection was consistently lower than provider-collected Papanicolaou tests, although on the whole sensitivity appeared to be better than the washing-type self-collection methods. One study directly compared a Davis-type washing device to the Kato brushing-type device, and found the Kato device to be more sensitive.[21] More robust studies would be necessary to demonstrate sufficient sensitivity for self-collection methods to serve as a stand-alone cytology screening test in the United States.

Studies on self-collection for HPV DNA testing are much more abundant. Multiple systematic reviews and meta-analyses seem to support similar sensitivity of self-collection to provider-collection.[34,35] Using a high-

Table 2 Studies of self collection, 1978 to present.

Study	No. women	No. abnormal	Self-collection device	Adequacy	EC present	Correlation	Sensitivity
						SCP to PCP	SCP versus PCP
Wash-style devices							
Arata et al[21]	122	NR	Lavage	86%-90%	NR	NR	SCC 80% versus 96% CIS 57% versus 93% Dysplasia 41% versus 71%
Given and Jones[22]	1151	364	MY-PAP ("douch-like device")	-[a]	NR	81.3%	SCC 94.6% versus 98.2% CIS 90.5% versus 95.2% Dysplasia 72.2% versus 81.5%
Nobbenhuis et al[23]	71	56	Lavage	NR	NR	41% $\kappa = 0.14$	42% versus 100%
Kuil et al[24]	171	NR	Lavage	91.5%	8.5% SCP versus 79.1% PCP	NR	33.3% versus 71.4%
Brush style devices							
Arata et al[21]	122	NR	Tampon (Kato)	95%-100%	NR	NR	SCC: 93% versus 96% CIS 83% versus 93% Dysplasia 59% versus 71%
Noguchi et al[25]	150	23	Tampon (Kato)	100%	NR	100%	-
Bernstein et al[26]	1428	202	Tampon (similar to Kato)	99.6%	NR	94%	SCC 100% versus 100% CIN3 89% versus 97% CIN1/2 81% versus 86%
Pengsaa et al[27]	552	13	Tampon (Kato)	NR	NR	99.6%	-
Garcia et al[28]	334	NR	Cytobrush	100%	34% SCP versus 86% PCP	76% $\kappa = 0.50$	CIN2+ 55.0%, versus 85.2% $\kappa = 0.50$
Pengsaa et al[29]	200	10	Tampon (Kato)	96%	NR	78% $\kappa = 0.61$	-
Budge et al[30]	209	85	Tampon[b]	NR	0% SCP	70%	38% versus 94%
Latiff et al[31]	258	7	Cervisafe® brushing device	100%	46% SCP versus 75% PCP	$\kappa = 0.62$	-
Latiff et al[32]	486	1	Tampon (Kato)	100%	23.4% SCP versus 90.5% PCP	100%	-
Recio et al[33]	272	[c]	Selfpap	-[d]	NR	83% $\kappa = 0.79$	80% SCP; PCP NR

Abbreviations: CIN, cervical intraepithelial neoplasia; CIS, carcinoma in situ; EC, endocervical cells; SCP, self-collected Papanicolaou test; PCP, provider-collected Papanicolaou test; NR = not reported; SCC, squamous cell carcinoma.

[a]Inadequate results by either device were excluded from the study; 100 total women with at least 1 unsatisfactory result, but not specified which technique.

[b]Ordinary Johnson and Johnson tampon placed in ThinPrep vial.

[c]Numbers appear to be reported inconsistently in manuscript so this could not be determined.

[d]Patients with unsatisfactory result by either method were excluded from analysis, but 1 unsatisfactory reported for each method.

sensitivity HPV assay (such as polymerase chain reaction) is important to achieving sensitivity similar to physician-collection, presumably because self-collection yields less viral DNA.[34] Overall, the data suggest feasibility of HPV self-collection for clinical use in the near future. In fact, self-collection is being offered nationwide in Australia for women who refuse a provider-collected sample as a component of its HPV-based national cervical cancer screening program, and a recent pilot study indicated a high patient acceptance rate with this approach.[36]

One of the remaining issues limiting the clinical use of self-collected HPV testing is triage of an abnormal HPV result. Pairing a self-collected specimen for HPV testing with a self-collected cytology (Papanicolaou) specimen would fit conveniently within the current guidelines for the management of abnormal Papanicolaou test results (cotesting).[37] An alternative approach under the current management algorithm would be to ask women with a self-collected positive high-risk HPV result (or the subset with non-16/18 high-risk HPV) to obtain a second, provider-collected specimen for cytology, but this would be significantly more inconvenient for patients, and more expensive, since a second collection kit and office visit would be required.[38] Alternative triage methods for HPV-positive patients, such as DNA methylation testing, have been studied in the specific context of self-collection, and a sufficiently specific method of triage could potentially abrogate the traditional role of cervical cytology in cancer screening in management of self-collected specimens.[39,40] Conversely, a self-collection method for both HPV and cytology could potentially leverage the high-sensitivity HPV component to overcome a lower sensitivity of the cytology component, and therefore might be more feasible than a stand-alone self-collection cytology device.

Large-scale clinical trials would be necessary to provide a robust level of evidence for FDA approval of a self-collection method in the United States, with sufficient numbers of abnormalities in the screened population, including high-grade squamous intraepithelial lesion and carcinoma, in order to confirm at least equivalency to provider-collection. This is necessary for confirmation of self-collection performance for both Papanicolaou tests and HPV tests. Importantly, just as the current FDA-approved liquid-based methodologies were approved by the FDA as a "test system," in which the entire collection, preservation, processing and evaluation process was tested as a whole, self-collection for cervical cancer screening must be similarly considered as an integrated test system, and the entire system interrogated for clinical non-inferiority to current provider-collected testing.

Is self-collection for cervical cytology achievable and reliable?

Historically, sampling of the cervical-endocervical transformation zone has been considered essential to cervical cytology. This assumption is logical because the great majority of carcinomas and their precursors arise in this location, and morphologic identification of virally affected cells is necessary to make a cytologic diagnosis of those lesions. Identification of endocervical cells or squamous metaplastic cells was a required component of adequacy assessment in early iterations of The Bethesda System for Reporting Cervical Cytology. In the original 1988 version, specimens without an endocervical component were termed "less than optimal" and in the 1991 edition this was changed to "satisfactory but limited by lack of endocervical component."[41] The presence of an endocervical component was revised from an adequacy requirement to a "quality indicator" in the 2001 edition of The Bethesda System[42] based on existing studies that showed no increase in false-negative rates in specimens without evidence of transformation zone sampling.[43-49] However, providers visually identify and target the cervical os when collecting a Papanicolaou test, so even when there is no cytologic evidence of the transformation zone, providers have a fair level of confidence that an area in the vicinity of the transformation zone has been sampled. In contrast, self-collection would be blind to the os. All of the studies that supported removing the endocervical cell component from adequacy criteria in The Bethesda System were based on provider-collected specimens, so these results cannot be extrapolated to self-collection methods.

For cytology self-collection to be viable, 1 of 2 options must be true: either the device must successfully sample the transformation zone, or cervical cytologic abnormalities must be detectable in spontaneously exfoliated squamous cells. Each of the studies shown in Table 2 that evaluated the presence of endocervical cells found a markedly reduced rate of endocervical cell sampling in self-collected Papanicolaou tests as compared with provider-collected tests, suggesting that most or all devices studied failed to consistently sample the transformation zone. Therefore, at least among the devices currently studied, sensitivity relies on the alternative condition—the presence of well-preserved spontaneously exfoliated cells with atypia sufficient to consistently make an accurate cytologic diagnosis. Although varying degrees of sensitivity have been recorded, whether non-transformation zone specimens can match the sensitivity of the provider-collected Papanicolaou test remains to be determined.

Would women use it?

Although self-collection potentially ameliorates several of the most commonly cited reasons for foregoing a Papanicolaou test in the unscreened/underscreened population, its longitudinal effectiveness in reducing cervical cancer in practice remains undetermined, and several factors suggest its effects may be limited in this population. The rate of underscreening has remained stubbornly resistant to a

variety of approaches and it is unlikely that any single intervention, in isolation, will have a major impact on improving cervical cancer screening.[50] A recent meta-analysis of self-collection studies for HPV found that participation in screening was improved in studies that directly delivered test kits to all women, but not in those where patients were required to take initiative, or "opt-in" to request a kit.[51] Because US screening is decentralized, it is hard to imagine a scenario in which a direct mail or other targeted outreach program would be possible on a large scale. Moreover, many of the cited barriers to care will persist even if self-collection is adopted and abnormal results are identified, and these barriers are likely to limit the potential for further management of abnormalities. For example, cost issues, lack of transportation, fear of doctors, and cultural barriers are likely to remain obstacles to care even in women with an abnormal self-collection result. In one study in rural Appalachian Kentucky, patient navigation conducted by nurses (which included assistance with scheduling appointments, transportation, and childcare services and attending the appointment with the patient) was utilized to encourage women to obtain Papanicolaou tests after self-collection for HPV testing, but only 7.5% had done so after 6 months, suggesting marked limitations in the ability to manage abnormal results in underserved populations.[52]

On the other hand, there are significant data from several studies on HPV self-collection to support the idea that a significant subset of currently screened patients would be enthusiastic to switch to a self-collection methodology.[6-8] One large survey found that 88% of women who had tried self-collection would prefer it to provider-collection.[9] A recent meta-analysis of 37 studies representing over 18,000 women found a pooled preference for self-collection by 59% of women.[8] We can anticipate that a significant number of women would switch from provider-collected to self-collected testing should this technology become available in the United States.

How would self-collection work?

Self-collection could be implemented in a variety of ways, each with benefits and drawbacks. The first major decision point is how self-collected cervical cancer testing would be ordered. Nearly all testing in the United States is ordered by a physician or other licensed provider, with the results reported back to the ordering provider. The benefits of implementing this approach for self-collected cervical cancer testing are obvious: It fits into existing patterns of workflow, it is in compliance with many state and federal regulations, and it ensures provider oversight of testing and results. In contrast, if the goal is to maximize uptake by the underscreened, who frequently do not have a regular provider, a self-ordered approach is more likely to achieve that goal. Home tests such as pregnancy testing and blood sugar monitoring are models of this approach, but those results can be interpreted by the individual at home, which is not the case with Papanicolaou testing. A better analogy is screening mammography, where patients may self-refer to a radiologist without a physician's order. Several complexities arise from this, including more responsibility for the radiologist to provide clinical care and guidance; the need to simplify reporting language so that patients can understand their test results; and the need to identify a referring provider to manage abnormalities if the patient does not have a primary care physician.[53] These issues would also apply to pathologists in this model.

Another decision point is home collection versus collection in a physician's office. Fecal occult blood testing, for example, is typically ordered by a physician but collected by the patient at home, whereas urine collection is more commonly done by the patient, but in the provider's office. Like self-ordering, home collection is likely to provide maximum convenience and comfort, and is thus likely to maximize uptake, whereas office collection allows for a more controlled environment, with a known collection date and time, control of specimen conditions such as temperature, limitation of access to potentially hazardous chemicals (eg, to prevent ingestion of the collection medium by a child), and easy access to clinic staff for education in proper use of the collection device. Presumably, self-collection in a provider's office would take place in the context of a routine provider visit, which may have benefits unrelated to cervical cancer screening.

Finally, the actual methodology of collection and testing must be determined, such as the sampling device, the collection medium, medium storage and transport requirements, patient instructions, and specimen delivery for testing. In the limited studies to date, none of these details has been standardized. Thoughtful consideration of the tradeoffs inherent in each of these decisions will be critical to maximizing the success of a self-collection-based cervical cancer screening test.

How would the testing laboratory be selected?

Some laboratory tests performed on cytologic material have been marketed directly to providers as a package with cytologic evaluation at a designated laboratory. The authors do not believe this mode best serves patients and providers because it limits choice and can create a monopoly that drives up cost. Preferably, the ordering individual (patient or provider) would have the flexibility to choose a laboratory to perform the cytologic evaluation of self-collected specimens. Laboratories have different pricing, turnaround times, quality assurance programs, customer service, and accreditation, and should be able to compete on the basis of these differences. Providers are generally comfortable deciding where to send laboratory tests, but this would be a new experience for patients, one that could be potentially overwhelming. It could also put laboratories in the novel position of marketing directly to patients rather than providers.

What are the pre-analytic issues with self-collection?

Several potential pre-analytic issues arise that are unique to self-collection. First, instructions for use must be clear and easy to understand, including for those who are illiterate or for those with language barriers. This is particularly important in the case of home collection, but would also be important for in-office self-collection. If the patient cannot collect an adequate specimen, a benign interpretation may not be reliable.

The performance characteristics of the transport medium are a key pre-analytic variable for home self-collection. The medium would have to be validated to preserve cells across a variety of environmental conditions, including extreme heat and cold during storage and commercial transport, or would need to be maintained in a controlled environment. The length of time that cells spend in the preservative could impact morphology and/or HPV testing. While laboratories never really know what has happened to a specimen before they receive it, the level of uncertainty would be greater for home self-collection, particularly if general mail options are selected. For instance, the patient might not accurately record the date of collection—perhaps she forgot to mail it in for 2 months and then changed the collection date so that she did not need to request a new test kit. Or maybe the specimen froze when the delivery truck broke down in severe winter weather. There are also strict requirements for shipping chemicals, such as alcohol, in the mail. In the absence of very thorough pre-market testing, these pre-analytic variables could create challenging issues for individual laboratories that are responsible for accurate results.

What are the analytic issues with self-collection?

Safety of the collection device and transport medium must be assessed before bringing a self-collection product to market, not only for the intended user of the device, but also for the safety of other household members, including children. Methanol-based fixatives, for example, have associated toxicity, and any alcohol-based fixative has flammability concerns. However, any changes to the collection device or transport medium made for safety or other reasons have the potential to affect cell morphology and therefore to alter standard diagnostic criteria. Just as training and certification is required for users of commercially available liquid-based Papanicolaou tests, any morphologic changes introduced by self-collection kits would likely require specific user training. Careful research would be needed to identify and characterize any differences prior to implementation.

Adequacy criteria represent another critical analytic concern. As discussed earlier, the current Bethesda System adequacy criteria are based on studies of provider-collected Papanicolaou tests obtained with direct visualization of the cervical os. Cytologists cannot distinguish a vaginal squamous cell from a cervical squamous cell; only the presence of endocervical or squamous metaplastic cells can distinguish a sample of cervical transformation zone from a sample of vaginal wall. Furthermore, all self-collection studies to date that have evaluated for the presence of endocervical cells have found a marked reduction in the number of specimens with endocervical cells compared with provider-collected Papanicolaou tests.[24,28,30-33] Adequacy criteria, then, cannot be assumed to be equivalent for self-collected testing. Rigorous, large-scale research studies would be required to determine whether specimens with only squamous cells obtained by self-collection are adequate for interpretation.

What are the post-analytic issues with self-collection?

Self-ordered self-collection would present a variety of complex post-analytic issues for laboratories. Laboratory report formats, including Bethesda System terminology, have been designed to make interpretation and management clear to medical professionals. The report language and format would require revision to maximize comprehension for patients at a range of English literacy levels, and perhaps in multiple languages, to ensure that findings are correctly understood. Reports would need to inform patients of the next necessary step in management, depending on the results. If taken seriously, this is a daunting challenge, especially since appropriate management is dependent on multiple factors such as prior history of dysplasia and other risk factors.

In addition, there are basic logistical issues to direct patient reporting. How should results be reported—by mail, phone, electronic means, or by multiple means? If by mail, the laboratory must somehow ensure that abnormal results are received by the patient. The laboratory must also ensure patient privacy, which becomes an immense challenge when others in the patient's household or at the patient's mailing address may have access to the report. If the patient moves, the laboratory is unlikely to get forwarding information and a result might be lost. If by phone, the patient may not remember the result long enough to act on it, and the follow-up provider would need a copy of the result, so an additional method would be needed. If by electronic means, some patients may not be able to access their results. Multiple means of reporting results may be necessary, but multiple contacts about the same result could also result in patient confusion. There are legal liability concerns as well: What is the legal liability for a laboratory that reports an abnormal result that does not reach the patient? What are the medicolegal obligations of a pathologist in terms of establishing a doctor—patient relationship by reporting abnormal results? Receipt of an abnormal result is only helpful to the patient if appropriate follow-up and management ensues. For patients

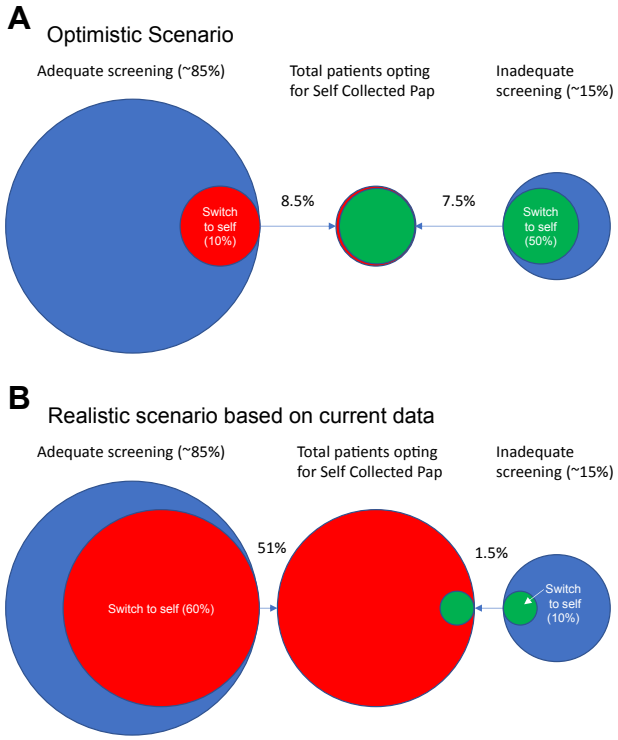

Figure 1 Proportion of women in the United States potentially affected by self-collected cervical cytology based on current screening. The area of each circle is proportional to the size of the population; the red and green circles from the right and left schematics are reproduced and overlapped in the center schematic for ease of comparison. A, An optimistic scenario, in which half of the women currently underscreened get self-collected Papanicolaou testing. In this scenario, if only 10% of women currently obtaining provider-collected Papanicolaou testing switch to self-collection, these women outnumber those gaining access. B, A more realistic scenario based on existing literature. In this scenario, only 10% or less of the currently underscreened population receive a self-collected Papanicolaou test,[52] while 60% of women currently engaged in provider-collected Papanicolaou tests switch to self-collection[8]; in this scenario, the number of women switching from provider-collection is 35 times the number of women benefitting from new access to self-collected Papanicolaou testing. Thus, a self-collected test with decreased sensitivity compared with provider-collected methods could do substantial harm.

who self-order and lack a provider, it could fall to the laboratory to provide a referral to a local provider.

How would Papanicolaou self-collection affect cancer rates?

Self-collection for cervical cancer screening presents an opportunity to reach a portion of the underscreened population and potentially reduce cervical cancer rates in the United States. It is clear that underscreening represents an important factor, probably the most important factor, in the residual cervical cancer incidence in the United States. Self-collection, particularly paired with self-ordering, could address many of the reported factors limiting some women's participation in Papanicolaou testing. As discussed previously, there are major challenges to implementation of self-testing in this population,[51] and also with follow-up of abnormal results.[52] On the other hand, approximately 83% of women in the United States undergo regular cervical cancer screening, and studies suggest high levels of interest in using self-collection technology among these women.[8,9] Thus, self-collection would likely have the effect of women "opting out" of provider-procured screening in favor of self-collection, and the majority of women adopting self-collected screening is likely to be those who are currently adequately screened (Fig. 1). It would be a mistake to implement a screening method less sensitive than the standard of care based on the hypothesis that it represents a major improvement over no screening among underscreened populations, because there is no way to restrict this collection method to that population. Therefore, it will be essential for any device approved for self-collection to be equally effective in comparison with existing screening to avoid inadvertently creating a situation in which the harms of self-collection outweigh the benefits.

It is important to think of cervical cancer prevention as a longitudinal series of interventions, rather than as a single screening test. Every Papanicolaou test result is subject to a complex algorithm of management that depends on age, pregnancy status, high-risk HPV status, clinical history, and prior Papanicolaou test and biopsy results. Even for a normal Papanicolaou test result, the appropriate timing of the next Papanicolaou test is dependent on a variety of factors. These complex management algorithms are confusing even to providers who use them regularly, and will no doubt be confusing to patients, who would have to assume responsibility for rescreening at appropriate intervals in a self-ordered, self-collected testing environment. Much of this information will be unavailable to the laboratory issuing the Papanicolaou test result, so the laboratory report cannot be the sole source of guidance for appropriate rescreening intervals. Given current prolonged screening intervals, it is likely that repeat Papanicolaou tests will be delayed or missed without the organization of follow-up physician visits, potentially further weakening the current cervical cancer prevention system in the United States. Even in countries with an organized national registry, women who consider themselves involved in the screening program may significantly delay or fail to undergo Papanicolaou tests due to the busyness of daily life.[54] Thus, any self-collection method requires well-designed mechanisms to provide for routine repeat cervical cancer screening at intervals appropriate to each individual.

Conclusion

Meta-analyses of existing studies of self-collection for HPV testing support the possibility, with high-sensitivity

methodologies, of achieving similar sensitivity to provider-collected HPV testing. The existing studies of cytology testing using Papanicolaou test self-collection devices are very limited in number, in study size, and in study design, and most find decreased sensitivity compared with provider-collected Papanicolaou tests. The literature does not support self-collected cytology testing at present. Nevertheless, there is likely to be intense interest in developing such a test, or an alternative triage test, to pair with self-collected HPV tests, in order to conveniently integrate self-collected HPV testing into current management guidelines. Self-collection has the potential to bring a segment of the underscreened population into a screening program, while providing a more comfortable and convenient approach for women who are regularly screening. Self-collected Papanicolaou testing, particularly if offered as a self-ordered, home-collected test, presents a variety of uniquely complicated challenges for laboratories, encompassing the pre-analytic (specimen collection and transport), analytic (potential changes to adequacy evaluation and diagnostic criteria), and post-analytic (result reporting and patient management) phases of testing. Additionally, most women adopting the test are likely to be women currently engaged in regular screening, so a less-sensitive screening regimen than the current standard of care has the potential to do significant harm. Large-scale, carefully designed, randomized clinical trials that evaluate any new technology as a system, from collection through resulting, will therefore be necessary to ensure that this potential new technology supports the tremendous progress, driven largely by the Papanicolaou test method pioneered by Dr Papanicolaou, made in prevention of cervical cancer in the United States.

Declarations of interest

None.

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