ZedScan delivers improvements in clinical performance and more efficient patient management at Sheffield Teaching Hospitals NHS Foundation Trust

Increased detection of high grade Cervical Intraepithelial Neoplasia (HG-CIN) both in women with HPV16 and non HPV16 related disease relative to colpscopy alone

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Updated March 2016 1570 patient evaluation

Summary Overview:

ZedScan™ has been incorporated into routine use in colposcopy at Sheffield Teaching Hospitals NHS Foundation Trust (STH). The service has completed over 1570 patient examinations and performance data has indicated improvements in accuracy and increased compliance with NHSCSP20 guidelines for performance.

- An additional 59 cases (13.25%) of high-grade disease were identified.
- There was a marked increase in the number of cases of high-grade disease detected in women referred with low grade dyskaryosis or borderline abnormalities from 86-129 (50% increase). In 92% of these cases, disease was confirmed with a single biopsy.
- Average biopsy rate per woman was 1.1 compared with the published value of 1.7[1].
- Colposcopy failed to identify 14.1% of all high-grade histology whereas only 3.8% of all high-grade histology was not identified by ZedScan.
- ZedScan outperformed colposcopy at detecting disease in hrHPV positive women irrespective of genotype.
- An additional 5 cases of HG CIN were detected in women who were cytology negative hrHPV positive, corresponding to an increase of 38.5%. 2 were HPV16 positive women, 2 HPV18 positive and 1 other hrHPV genotype.
- The 'See and Treat' rate has increased from 36-39% in previous years to 68% of all high-grade referrals; high-grade disease was confirmed in 95.2% of the cases exceeding the value of 90% PPV indicated by the NHSCSP20 guidelines[2].
- There has been a decline of >40% (from 676 in 2012/13 to 374 in 2014/15) in the number of follow up appointments since the introduction of ZedScan.

Improved patient outcomes and advancements in efficiency are evident following adoption of ZedScan into routine use.

Introduction

Sheffield Teaching Hospitals NHS Foundation Trust (STH) is a tertiary referral centre providing a colposcopy service for women referred with abnormal cervical screening results or clinical conditions requiring further investigation.

The cervical screening departments, comprising the histology and cytology laboratories along with the colposcopy, are considered centres of excellence with members frequently consulted by the NHSCSP National office to advise and contribute on the national guidelines. In addition several hold or have held senior positions in relevant professional societies and are well respected by their peers.

As a regional centre, the service encompasses a wide geography, processing samples and accepting referrals from across the whole of South Yorkshire.

In 2014-15, the cytology lab examined 85,084 samples. Following abnormal cytology result, 2526 women were referred to colposcopy for further investigation with 536 women receiving treatement for HG CIN during this period.[3]

As one of the six sites in England currently evaluating primary HPV screening, STH has seen a substantial increase in the number of colposcopy referrals. Like many centres across the UK, colposcopy at the Jessop Wing, is a nurse-led service, operating up to 15 clinics per week, with an average attendance of 8-9 patients per clinic. To cope with the increase in referral numbers, the centre looked to new technology and changes in practice as a means of improving efficiency and increasing compliance with NHSCSP guidelines.

STH Colposcopy team (L-R, Rachel Wild, Rachel Lyon, Joanne Rymell, Dr Julia Palmer lead colposcopist, Prof John Tidy)

Introduction of ZedScan™ into routine clinical practice.

The ZedScan™ system was introduced into routine clinical use in 2014 to provide the colposcopy team with additional information to support more effective patient management.

Data from 1570 women attending colposcopy between January 2014 and December, 2015 were analysed. These women had a colposcopy + ZedScan examination. 401 patients (25.5%) were referred with a high grade cytology (moderate dyskaryosis or worse) and 836 (53.2%) with a low grade cytology (borderline and low grade dyskaryosis). The remaining 333 (21.0%) consisted of women who were positive for hrHPV, clinical referrals and women who were being monitored following a previous diagnosis of CIN.

The examinations were conducted by a team of 5 clinicians comprising 3 nurse colposcopists and 2 consultants, with >93% of the examinations conducted by the nursing staff.

Results:

Increased detection of High Grade CIN

504 women in total had histologically confirmed high grade CIN (HG CIN). (Table 1a)

Of these, both ZedScan and colposcopy agreed HG CIN was present in 426 (84.5%) women with ZedScan alone detecting an additional 59 patients, representing a 13.25% increase in the overall rate of detection (Table 1b). There was a marked increase in the number of cases of high grade disease detected in women referred with low grade dyskaryosis or borderline abnormalities from 86 to 129 (50%).

- Colposcopy failed to detect 14.1% of cases of HG CIN whereas only 3.8% of cases were not detected by ZedScan.

Table 1a: Increase in detection of HG CIN

HG CIN confirmed	No. of Women	Sensitivity
ZedScan & Colposcopy agree	426	84.5%
Colposcopy alone	433	85.9%
ZedScan alone	485	96.2%
All	**504**	**100%**

Table 1b: Breakdown of patients with HG CIN by cytology referral

Cytology	HG CIN (CI + ZedScan)	Additional cases detected by ZedScan	Increase in detection rate Sensitivity
High grade	337	10	3.1%
Low grade	129	43	50.0%
Other referrals	38	6	18.8%
Total	**504**	**59**	**13.25%**

In order to determine the absolute sensitivity random biopsies would be required on all women.

In this analysis sensitivity has been calculated based on normal colposcopic practise, where biopsies have been taken according to colposcopic impression and ZedScan result. (Table 1a)
A woman is only considered as positive following histological confirmation of HG CIN.

These data reinforce the clinical benefits of integrating ZedScan into the colposcopy examination, reducing the incidence of missed disease and enabling HG CIN to be detected and treated. (Table 1b) Without the use of ZedScan these women would not have been identified until either a subsequent colposcopy appointment or a repeat cervical screening test in the community.

- Use of ZedScan as an adjunct to colposcopy increased the overall detection of high grade CIN by 13.25%. The increase was 50% in women with a low grade cytology referral.

Patient Management: HG CIN- 'See & Treat'

278 women were treated at first visit with 262 (94.2%) confirmed as CIN2+. (Table 2)

Of these patients, 261 were identified by ZedScan as being suitable for 'See & Treat' and 249 (95.4%) were confirmed histologically.

The remaining 17 women were positive for HG CIN both by ZedScan and colposcopic impression, but below the ZedScan threshold for 'See & Treat'. The clinicians decided to treat on colposcopic impression. 13 were subsequently confirmed as CIN2+, 2 returned a histology of CIN1, one was reported as LG-CGIN and one was reported as normal.

Of the 401 women who were high grade referrals, 259 underwent 'See and Treat' of which 247 (95.4%) were confirmed with disease.

During the period covered by this analysis, the 'See and Treat' rate for women referred with high grade cytology has increased from 33-39%, in previous years, to 68% which is significantly higher than the national rate of 50.4%.

Four women had low grade cytology; two had low grade dyskaryosis and two were borderline glandular referrals. Of the four, one had HG CIN, one case of LG-CGIN was identified, one was CIN1 and one was reported as normal following histological analysis.

- The use of ZedScan as an adjunct to Colposcopy enabled 17.7% of the patients referred to undergo See & Treat with a PPV of 94.2%. The See & Treat rate for high grade referrals was 68% with a PPV of 95.4% complying with NHSCSP guidelines.

Table 2: Performance data for 'See & Treat'

All referrals	No of women treated	HG CIN confirmed	PPV
CI + ZedScan S&T	278	262	94.2%
ZedScan S&T	261	249	95.4%
High Grade referrals	**No of women treated**	**HG CIN confirmed**	**PPV**
CI + ZedScan S&T	273	260	95.2%
ZedScan S&T	259	247	95.4%

Extending the role of See & Treat

In addition to the 278 women treated at first visit ZedScan identified a further 212 patients for whom 'See & Treat' was indicated, but the clinical decision was to take a directed biopsy.
Of these 212 patients 73 were HG referrals and 95 LG referrals. The biopsy confirmed CIN2+ in 55 and 74 of these groups respectively. Performing LLETZ on all the additional women indicated for 'See & Treat' by ZedScan would reduce the PPV below the NHSCSP guidelines, however if 'See & Treat' was only offered to HG referrals, a total of 346 procedures would have taken place with 315 (91%) confirmed as CIN2+ (Table 3).

Table 3 shows the potential for extending 'See and Treat' based on the additional information provided by ZedScan.

Nurse colposcopist Rachel Wild using ZedScan during colposcopy examination

Table 3: Comparison of performance for potential additional See & Treat cases identified by ZedScan

Referral Cytology	See & Treat ZedScan/CI	Additional cases suggested as suitable by ZedScan	Total	CIN 2+	PPV
All referrals	278	212	490	391	79.8%
High grade referrals	273	73	346	315	91%

- There is the potential to widen the application of See and Treat to more women with high grade cytology where indicated by ZedScan

Patient Management: Directed Biopsy

In total, 688 of the 1570 women underwent biopsy directed by colposcopy, ZedScan or both. 241 had confirmed disease of which 128 were women referred with low grade cytology. In 29 of these patients disease was only indicated by ZedScan.
In total 746 biopsies were taken with an average of 1.08 biopsies per biopsied patient.
More than one biopsy was taken in 53 patients.

In terms of patient management, low grade referrals are often the most difficult to assess and constitute the highest proportion of women undergoing biopsy.

- The inclusion of ZedScan as part of the colposcopic examination has demonstrated particular benefit in detecting disease in low grade cytology referrals accounting for an additional 50% of women with HG CIN who would not otherwise have been identified. This increased detection of disease was achieved with only one biopsy in 92% of cases.

Table 4: Women undergoing biopsy

Referral Cytology	No. of Women	Biopsy proven HG CIN
High grade	125	77
Low grade	431	128
Other	132	36
Total	**688**	**241**

Detection of hrHPV related disease

The presence HPV16 has been associated with more obvious aceto-white change in the cervical epithelium,[8] causing expectations of reduction in the performance of colposcopy in detecting HG CIN, due to epidemiological changes following vaccination.

As one of the sentinel sites using HPV testing as the primary screen, the results were also evaluated on the basis of their HPV status to profile the ability of ZedScan to detect disease in hrHPV positive women.

All Patients

Of the 1570 patients examined, HPV genotyping data was performed on only 839 women. 265 were confirmed with HG CIN. Colposcopy was better at detecting disease in HPV16 positive patients (86.9% sensitivity) compared to those who were positive for other hrHPV genotypes. (79.7% sensitivity)

Performance of colposcopy with ZedScan outperformed colposcopy alone at detecting disease irrespective of HPV genotype. (see Table 5)

hrHPV positive, cytology negative

228 patients were referred as hrHPV positive but cytology negative, for which the HPV genotype was identified for 187 women.

In total ZedScan identified an additional 5 cases of HG CIN (Table 6) representing an increase of 38.5% in detection.

- Use of ZedScan alongside colposcopy was more effective at identifying disease than colposcopy alone, in all hrHPV positive women and in particular non HPV 16 cases. The addition of ZedScan increased the detection of CIN2+ by 38% in women who were referred with hrHPV positive, cytology negative screening results.

ZedScan compensates for reliance on acetowhite change to colposcopically identify disease, providing a more reliable and effective diagnosis This will be of particular benefit as the prevalence of HPV16 and HPV 18 related disease falls in vaccinated populations.

Table 6

hrHPV	Number	CIN2+	Additional cases of CIN2+ identified by ZedScan
HPV16	82	12	2
HPV18	34	3	2
HPV Other	71	3	1
Total	187	18	5

Detection of Glandular Disease

In total 18 women were found to have histologically confirmed glandular disease, 14 of which were diagnosed as having no co-existing HG CIN (Table 7).

Seven of 14 women were positive by both ZedScan and colposcopy, 2 were positive by colposcopy only and 5 were positive by ZedScan only.

The low incidence of glandular disease precludes any statistical validation of performance, nevertheless there is evidence to support the use of ZedScan for detection of HG CGIN.

Table 7

CGIN only	CI positive	ZedScan positive
14	9 (64%)	12 (85.7%)

Table 5

HPV status	Total	CIN2+	CI positive	ZedScan positive	Additional cases of CIN2+ detected by ZedScan	P value
HPV 16	303	137	119 (86.9%)	131 (95.6%)	13 (10.5%)	P=0.0171
hrHPV (non 16)	536	128	102 (79.7%)	124 (96.9%)	21 (19.6%)	P<0.0001
All hrHPV	839	265	221 (83.4%)	255 (96.2%)	34 (14.7%)	P<0.0001

Patient Management: Negative Predictive Value

561 women were negative by ZedScan. Of this group 19 women were considered positive by colposcopic impression of which 7 were confirmed by biopsy. These figures can be used to calculate the Negative Predictive Value (NPV) for ZedScan as 98.7%. The comparable figures for colposcopy alone are that 958 were negative. Of these 416 were positive by ZedScan and 59 were confirmed by biopsy. The NPV is thus 93.8%. However, these figures for NPV can be misleading as there could be women with disease who were not subject to biopsy.

There were 58 women who were considered negative by both colposcopy and ZedScan but who none-the-less underwent a colposcopically directed biopsy. 10 of these women were confirmed as having HG CIN (NPV 82.8%). The fact that these 58 women had a biopsy suggests that the colposcopist wanted to exclude disease and hence we would expect the NPV to be higher than 82.8% in the remaining 545 women where no biopsy was taken.

It is not possible to determine the Negative Predictive Value of ZedScan as an adjunct to colposcopy from this cohort of patients because biopsies were not taken in all the women. However, we can estimate the NPV as lying between the 82.8%, found in the group of women with a negative test but where a biopsy was taken, and the figures of 93.8% and 98.7% found for the whole cohort of women.

- These figures can offer reassurance when the colposcopist wishes to release a woman back to routine surveillance.

Discussion

Impact on clinical pathway

The objectives of colposcopy are to identify and treat women with HG CIN and exclude the presence of HG CIN in women referred with minor cytological abnormalities or persistent hr HPV positivity.

Analysis of the performance data evaluated since the introduction of ZedScan, has demonstrated unequivocal improvement in the ability to identify and detect high grade disease. (Table 8)

While many colposcopy clinics offer a ‘See and Treat’ option for selected women other colposcopy clinics will prefer to confirm disease with biopsy before offering treatment.

In some situations there are clinical reasons for not offering treatment. In deciding how to manage each woman with HG disease, the colposcopist will take into account the age of the woman, her desire to have more children and balance this with the risk of potential complications before making the decision to offer treatment.

The inclusion of ZedScan at STH has demonstrated high levels of performance in correctly identifying women with disease and in particular those for whom treatment at first visit is an option. Following the addition of ZedScan at STH, the colposcopy team are now more confident in accurately deciding when to perform ‘See & Treat’.

The majority of women referred to colposcopy at STH are low grade referrals, 55.8% of cytology referrals in 2015, and these are patients for whom the inclusion of ZedScan has demonstrated the greatest benefit.

Table 8: Performance analysis on 1570 patients

	Histopath + CI result		Sensitivity	100%
ZedScan+Colp	Positive	Negative	Specificity	55.6%
Positive	504	463	PPV	52.1%
Negative	0	603	NPV	82.8-98.7%
Total	**504**	**1066**	Balanced Accuracy	77.8%
			+LR	2.25
			DOR	656

Results are available immediately on completion of the examination.

Management of women with low grade cytology can be challenging for colposcopists with colposcopic examination and biopsy results often inconclusive, potentially requiring many women to undergo repeat examination within 6-12 months. Similarly, with the introduction of HPV DNA testing, even when colposcopy indicates no visible evidence of disease, clinicians may be reluctant to discharge women who test positive for hr HPV due to concerns over missing disease, contributing to the number of women being recalled.

For these women, ZedScan has reduced the ambiguity, identifying both where disease is present and also clarifying patients who can safely be discharged, with up to 98.7% NPV. As a result, follow up rates at STH have continued to decline, with a reduction of more than 40% compared to previous years before the introduction of ZedScan.[7]

Health Economic impact:

Release of clinic time

Integration of ZedScan into routine use has created the opportunity to release clinic time by reducing the number of patients returning for follow up appointments.

The increase in the rate of S&T from 36-39% up to 68% of high grade referrals reduced the number of follow-up appointments for treatment by 164 in the period of this study. If 'See & Treat' was also offered to those women with a high grade referral identified by ZedScan as suitable for treatment, then a further 68 appointments would have been released while still maintaining a PPV in excess of 90% for HG CIN.

In addition to this, if all 603 women identified during the study period as having no HG disease were discharged, an additional 76 clinics could have either been released or accommodated new patients. There may be clinical reasons for recalling a woman rather than discharging. If only those patients for whom both ZedScan and colposcopic opinion indicated no HG CIN, then 542 appointments could potentially be released, equivalent to approximately 68 clinics.

In practice, we can see that compared to the last full reporting year before the introduction of ZedScan (2012/13), there had been a 44.7% reduction in follow-up appointments by 2014/15, when ZedScan was in use (from 676 down to 374).

Examination Time

With 20-30 minutes allocated for each patient attending colposcopy, there were initial concerns that use of ZedScan would increase the time required to complete the examination and impact on patient throughput.

During the learning curve period, an extra 5-10 minutes was allowed for lack of familiarity with the ZedScan workflow. After examining 10-20 patients, the colposcopy team reported completion of the initial 10-12 ZedScan measurements within 2-3 minutes, adding minimal time to each appointment and exerting negligible impact on clinic throughput.[7]

Reduction in histology burden

The changes in patient management following adoption of ZedScan also exert a corresponding impact on the histology workload.

Of the 1570 women examined, a total of 746 biopsies were taken from 688 women, equating to 44% of the women attending at an average of 1.1 biopsies per woman. This compares favourably to the STH data for 2013-143 where 55.4% of new referrals were reported as having had diagnostic biopsy, suggesting a significant decrease in the number of women undergoing biopsy following the introduction of ZedScan.

For low grade referrals 431 (51.5%) women underwent biopsy at a rate of 1.06 per woman substantiating the improved detection rate as attributable to ZedScan rather than an increase in the number of directed biopsies taken.

Comparison with Clinical Trial Performance.

To make a comparison with published performance from the BJOG, March 2013 clinical trial, only those patients (1237) who were referred with an abnormal cytology (401 HG, 836 LG) were included. (Table 9)

In this evaluation of routine practice the percentage of women referred with HG cytology was lower when compared with the BJOG trial (27% vs 44.4%). There was also a significant reduction in the prevalence of HG CIN (32% vs 44.4%, p<0.001). The positive predictive value of a test will fall if the prevalence of the disease also falls unless the performance of the test is improved. There was no fall in PPV in this evaluation when ZedScan was used as an adjunct to colposcopy which reflects the improved performance of the combination of ZedScan and colposcopy compared with colposcopy alone. Sensitivity, specificity and balanced accuracy are not dependent on the prevalence of disease in the studied population and so can be used to predict the performance of ZedScan in similar clinical settings.

Table 9: Comparison with BJOG clinical trial performance data

	Colposcopy Clinical Trial (BJOG, 2013) N=196	Colposcopy plus ZedScan, Jessop wing, STH. N= 1237
Sensitivity	88.5% (95% CI 79.9-99.4)	100%
Specificity	38.5% (95% CI 29.4-48.3)	52.1%
PPV	53.5% (95%CI 45.0-61.8)	55.8%
NPV	80.8% (95% CI 67.5-90.4)	97.8%
Accuracy	63.5% (95% CI 51.6-75.4)	76%
+LR	1.43 (95% CI 1.24-1.69)	2.09
Prevalence of HG cytology	44.4%	32%

Longitudinal Analysis

Review of patient management over the 2 year period has highlighted the impact of adopting ZedScan on the colposcopy service at STH.

Referral Population

- Colposcopy referrals have increased by 60% from 1576 in 2011/12 to 2526 in 2014/15 (Figure 1).
- The highest proportion of referrals continue to be from women with low grade cytology however there has been a substantial increase in hrHPV referrals. These accounted for approx. 69% of the Non Cytology Referral group at 24 months compared to 28% at the 12 month period. The decline in clinical referrals is a result of a modification to the clinical pathway as these are now managed within a separate clinic (Figure 2).

Improvements in Detection Rate

- The increase in detection of HG disease has grown from 11.2% after 12 months to 13.25% after 2 years. The highest proportion of additional cases comes from low grade referrals where the improvement has increased from 36.8% up to 50% within the past 12 months.

Figure 1

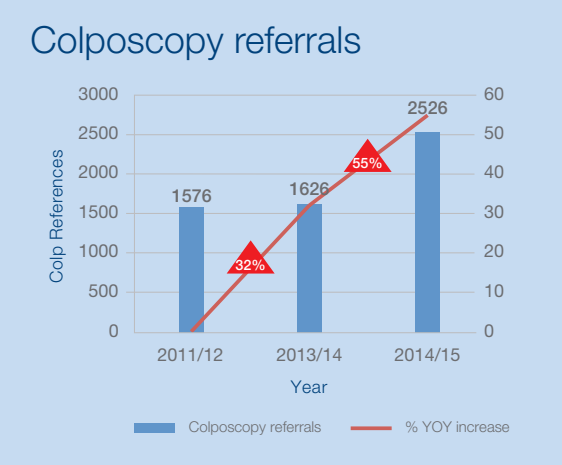


Figure 2

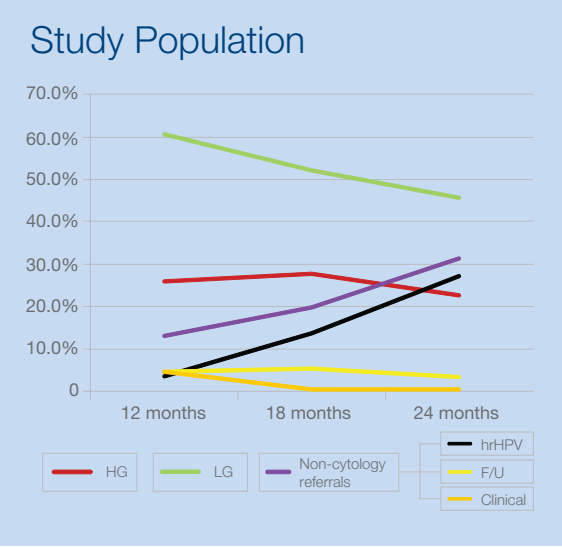
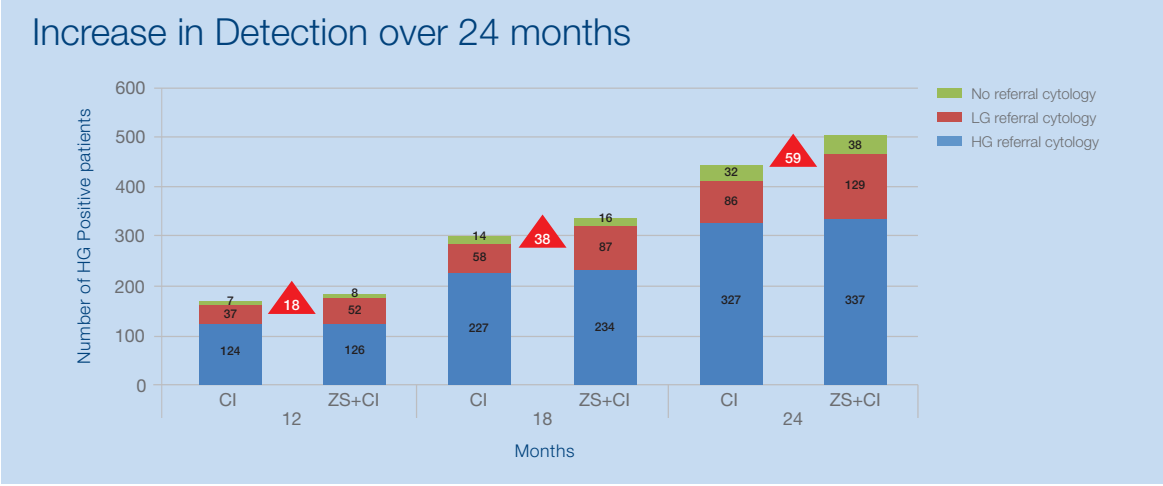


Figure 3



Patient Management

See & Treat

- See & Treat rate has increased from 12% of all referrals before implementing ZedScan to 17.7% of all referrals 24 months post implementation (Figure 4). For high grade referrals this has increased from 36-39% to 68% of all HG referrals, compared to the national rate for 2014/15 of 57.7% ($p<0.001$)

There has been no reduction in the histological threshold as a result of the increase in See & Treat as the proportion of CIN3 identified in See & Treat patients has remained high at 85%. As the rate of CIN3 has remained fairly consistent, over treatment of CIN2 can be excluded as a consequence of increasing the rate of See & Treat (Figure 5).

Biopsy

- The rate of patients undergoing biopsy has fallen from 52.5% before the introduction of ZedScan to 40.4% after 2 years of routine use (Figure 6).

  This is directly attributable to the increase in patients having treatment at first visit in addition fewer patients being biopsied because they are negative by both ZedScan and colpsocopy.

Outcome

In the 2 years since adoption, ZedScan has delivered the anticipated improvements in accuracy and efficiency enabling the colposcopy service at STH to accommodate the increase in referrals through better patient management.

Figure 4

Figure 5

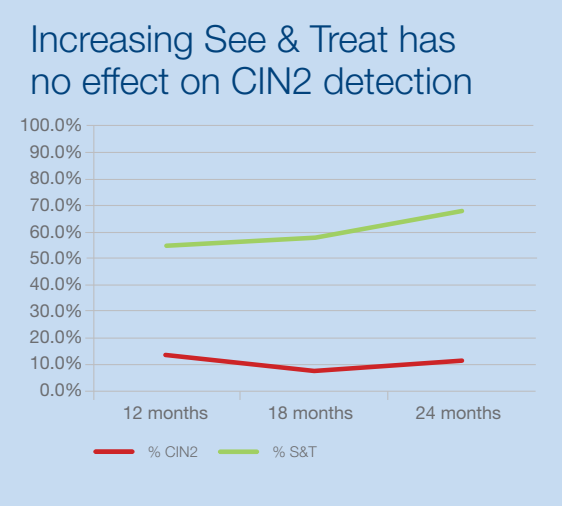
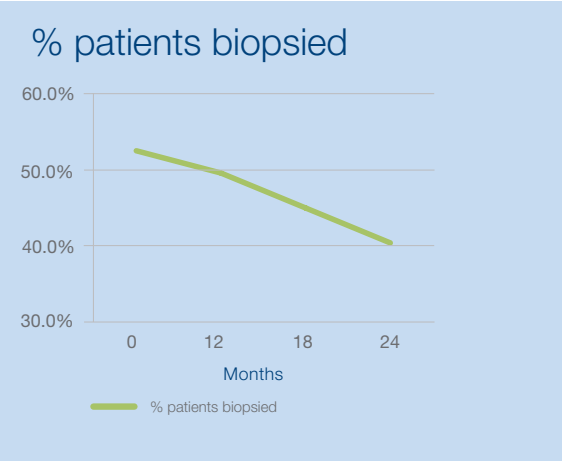


Figure 6



Conclusions:

The introduction of ZedScan as an adjunct to colposcopy has enabled STH to provide an improved service in terms of better patient management and health economics.

The achievement of higher rates of detection at first visit without a corresponding increase in biopsy has minimised the risk of un-necessary procedures and supports the use of ZedScan in generating better patient outcomes.

Efficiencies are also starting to be realised as confidence in making the decision to treat or discharge at first visit has grown. This is particularly evident in women with a low grade cytology, constituting 56% of all referrals, where ambiguity is reduced as a consequence of integrating ZedScan into routine clinical use.

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