Trinity College Dublin
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# AN EVALUATION OF THE QUALITY IMPROVEMENT POTENTIAL OF COMPUTER ASSISTED SCREENING TECHNOLOGY WITHIN A CERVICAL CANCER SCREENING PROGRAMME

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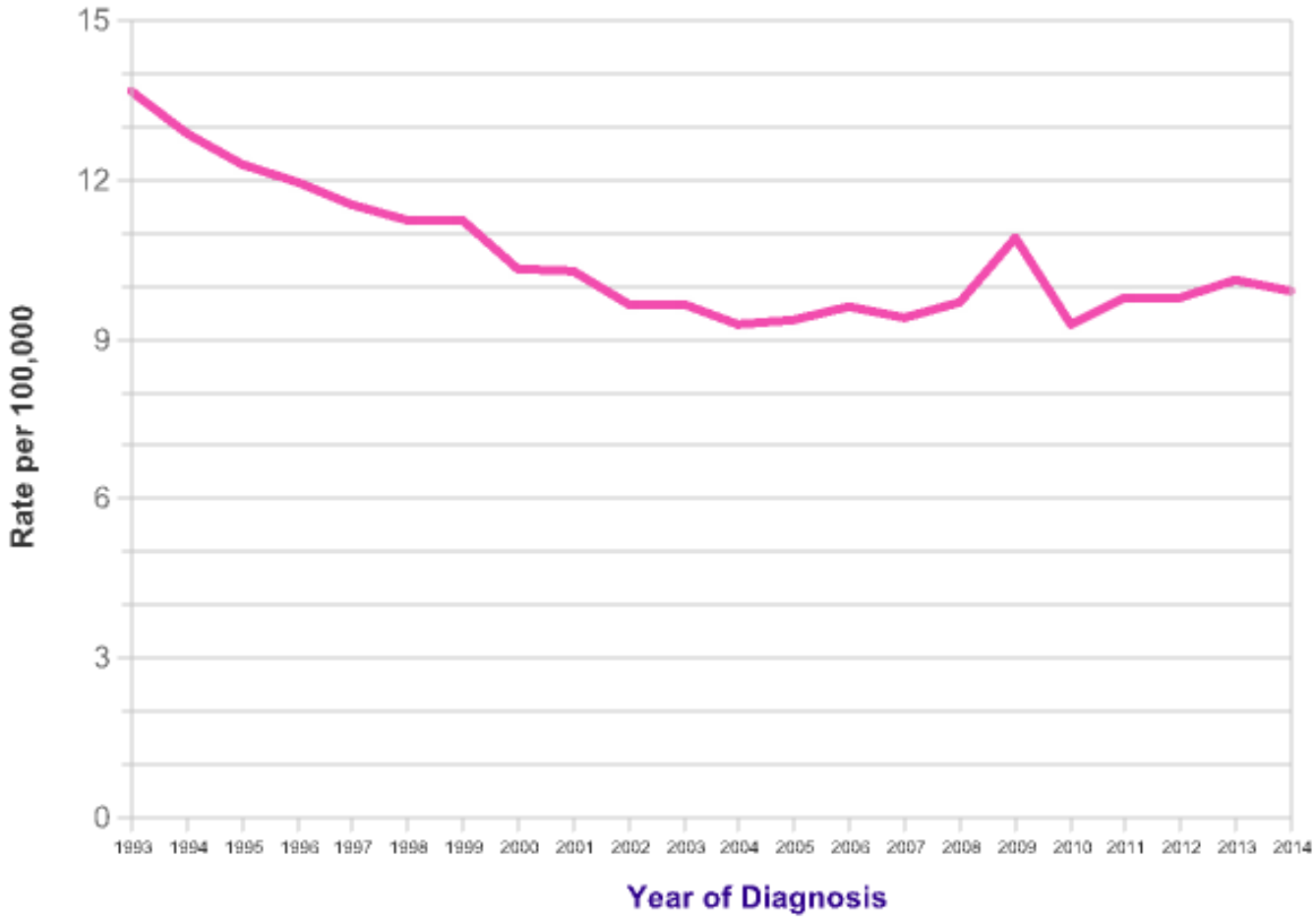
# Cervical Cancer: Definition and Development

- **Cervical cancer is a malignant neoplasm of the cervix uteri**
- **In 2012, 528,000 cases were reported worldwide with 266,000 deaths (WHO, 2014)**
- **In the UK, mortality in 2012 at a low of <5 deaths per 100,000**
- **However, in 2014, EASR mortality rates increased by 5% in the UK**
- **Worldwide, without urgent attention, mortality is projected to increase by 25% (WHO, 2014)**

# Cervical Cancer Incidence EASR 1993 - 2014



# Epidemiology of Cervical Cancer

- **Cervical cancer incidence exhibits strong birth cohort affects (Sasieni, Adams 2000)**
- **As a result, incidence increases with age, related to exposure to Hr HPV**
- **The incidence of cervical cancer increases rapidly between 30 and 40, and on up to 55 and then decreases steadily**
- **Cumulative risk to women born in the 1960s is 4-5%, emphasising the need for screening**

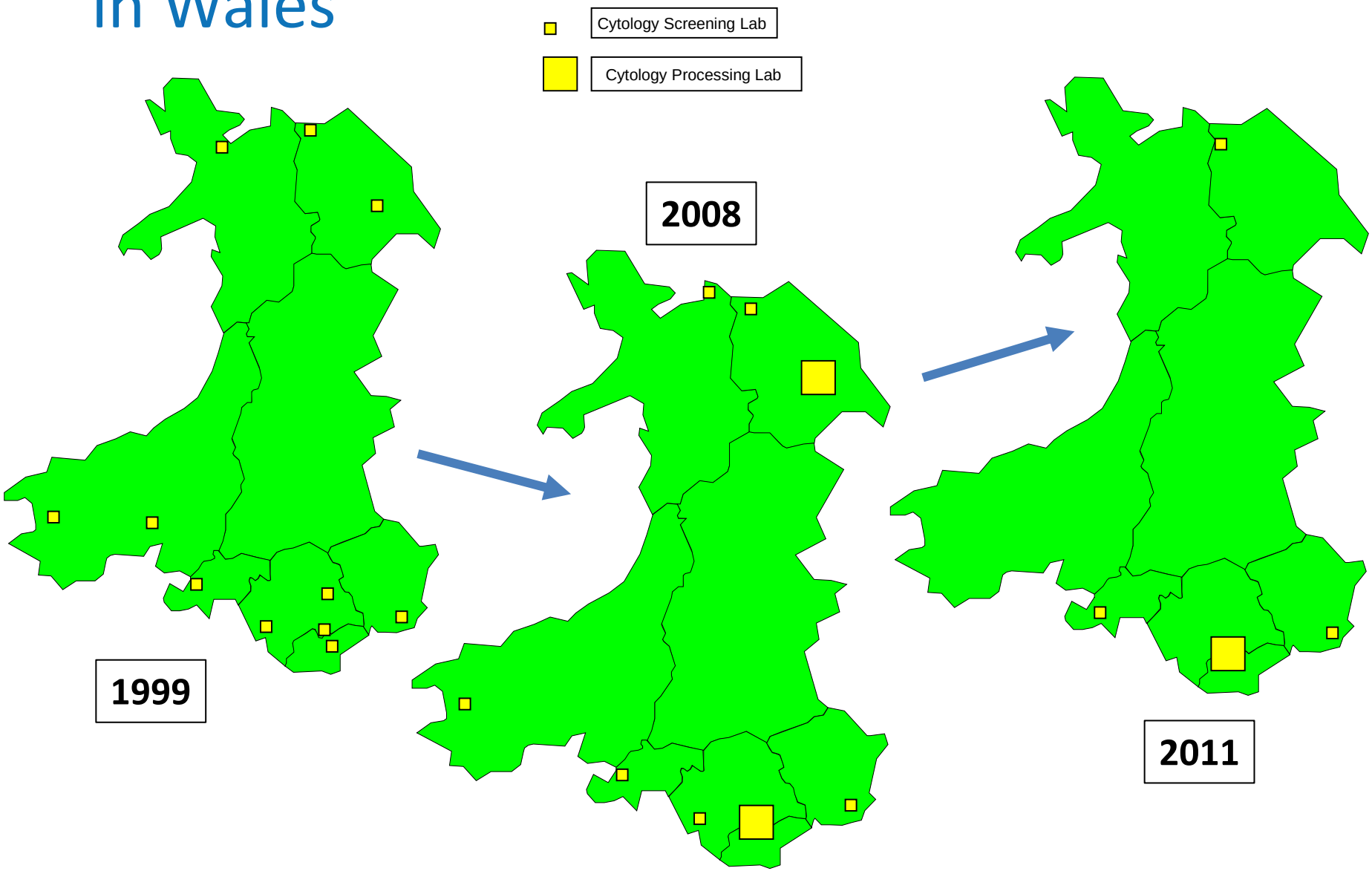
# The NHS Cervical Screening Programme

- **NHS CSP has operated a call and recall programme since 1988**
- **Estimated to have saved as many as 5000 lives annually (Peto et al., 2004)**
- **Using new technology to improve service quality and efficiency - a key strategy of the NHS CSP**
- **Introduction of LBC in 2004 reduced repeat tests from 9% in 2004-5 to 2.9% in 2007-8 (Kitchener et al., 2011)**
- **Further reduction in repeat testing since introduction of HPV Triage and ToC (HPV Sentinel Sites Pilot Implementation Project 2008)**

# The National Service Framework for Cervical Screening in Wales

- **1998 White Paper on NHS in Wales "Putting Patients First" announced an NSF for cervical screening**
- **Prime objective: "all eligible women received the level of service and quality of care for the same level of need"**
- **The Welsh Office and Velindre NHS Trust collaborated to create "Cervical Screening Wales"**
- **CSW launched in 1999**
- **At the time of this study, CSW invited women from 20 – 64 years for 3 yearly screening**

# Reconfiguration of Cytology Laboratories in Wales



# New technology as a means to improve service quality and efficiency

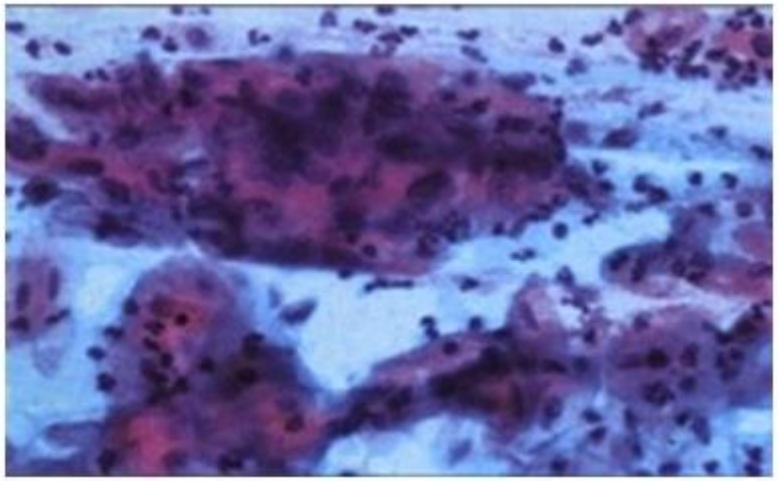
- **CAS (BD FocalPoint™ NFR) was introduced within the NHS CSP in 2013 (Denton et al.) and is currently in use**
  - Expensive technology requiring a critical minimum workload to maximise service quality and economic benefits
- **HPV primary screening will be implemented in 2019, which will impact on laboratory configuration with fewer staff required to deliver a reflex cytology "Test of Disease"**
- **Laboratory services will be reconfigured to make them larger and more efficient**
  - Deliver critical mass for quality reflex cytology testing
  - Impact on HPV workload depending on HPV positivity rates

# Why was this research conducted?

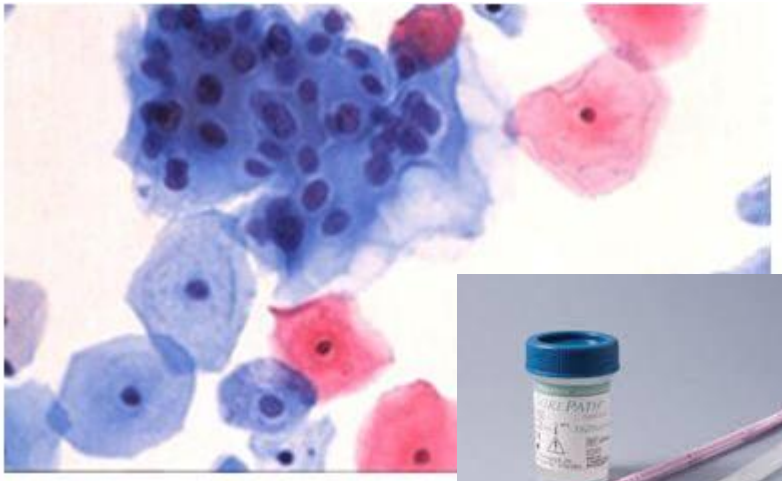
- **CAS viable once LBC introduced – offered by the main LBC providers**
- **Introduction of a 14 day turnaround time on the cervical screening programme in 2008**
- **Recruitment of cytotechnologists already an issue in the UK**
- **Cervical Screening Wales needed to validate CAS for the cervical screening programme in Wales**
- **Given relatively small size of Welsh labs – opportunity to evaluate CAS in a "hub and spoke" setting**
- **This networking strategy would maximise staff engagement around the principality**
- **Uses the high throughput capacity of CAS and HPV technology to maximum advantage**

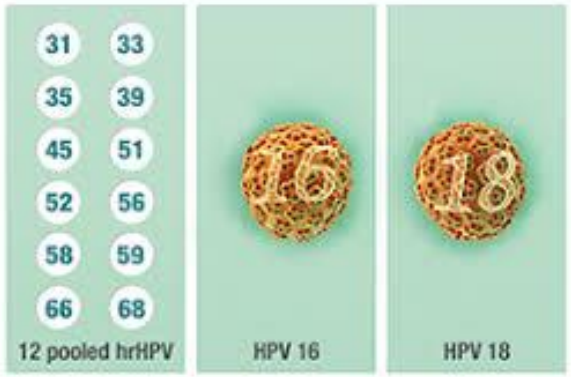
# Technologies in Cervical Screening

## 1964 - Conventional Cytology



## 2004 - Liquid based cytology






## 2011 - HPV testing (Triage and ToC)

# Development of CAS Technologies

- **Early European experiments involved the automated detection of DNA and RNA in Feulgen stained preparations**
- **Followed by the development of the Cytoanalyser by the Airborne Industries Laboratories in Mineola, New York, USA (Tolles, 1955) – designed to compare cell size as well as nuclear size and density**
- **Early researchers found that the complexities of automated morphological analysis and recognition very challenging……..**



Milestones in CAS Technology


# Development of CAS Technologies – the challenges for cervical screening

- **Similarities between benign and abnormal cells outweighed the differences**
- **Because of inadequate computing resources – processing the morphological data generated from several thousand cells on a Pap slide proved impossible at that time**
- **Thick, 3D clusters of cells compounded the problems**
- **Detection of nuclear:cytoplasmic borders was problematic**

# CAS – where are we?

- **The use of CAS is well documented in the US and Europe and has undergone several major trials – including MAVARIC***
- **CAS was investigated in Scotland and Ireland as well as in Wales - the Welsh CAESAR studies form the basis of my thesis**
- **Of the major trials, only MAVARIC reported that CAS offered no advantages over manual screening**
  - …but the No Further Review (NFR) component of the BD FocalPoint™ warranted further investigation
- **MAVARIC's findings not challenged since**
  - …mainly because the quality of the UK screening programme is one of the highest worldwide – the bar was set very high

* Kitchener HC, Blanks R, Dunn G, Gunn L, Desai M, Albrow R, et al. Automation-assisted versus manual reading of cervical cytology (MAVARIC): a randomised controlled trial. Lancet Oncol. 2011 Jan;12:56-64.

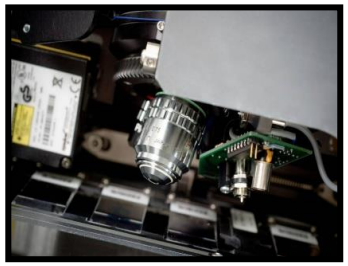
# CAS – where are we?

- **Rebolj et al. (2015), report better performance, but note performance variation between systems**
- **Renshaw and Elsheik, (2013) considered that work throughput demands for directed screening systems is a quality limiting factor**
- **Colgan et al. (2013) found that the efficiency of the detection of high and low grade lesions is variable**
- **The results of the CAESAR studies are presented and discussed in this thesis**

# Cervical Cytology and Computer Assisted Screening

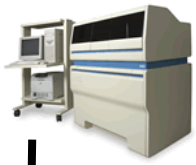
- **Conventional manual Cervical Cytology is carried out by specialist staff using light microscopy**
- **Cytotechnologists interact with the technology in varying degrees, depending on the product**
- **Two systems currently available:**
  - ***Becton Dickinson(BD) FocalPoint™ GS Slide Profiler***
  - ***ThinPrep™(TP) Imaging System (TIS)***
- **This study is primarily concerned with the BD FocalPoint™ GS Imaging System**

# BD FocalPoint™ GS Slide Profiler



Loading

Scanning



Data transfer via Removable hard-drive or VPN connection

GS Review Station

Image and Data Transfer to Operator

Server PC

Connectivity and Operation

- **Detects evidence of Squamous Carcinoma /Adenocarcinoma and usual precursor conditions**
- **Up to 300 features are analysed by morphometric and densitometric algorithms, including:**
  - Nuclear size
  - Nuclear shape
  - Nuclear texture (chromatin)
  - Cytoplasmic features
  - Nuclear density
  - Nuclear:cytoplasmic ratio
  - Contrast
- **Scans, sorts and ranks slides in values between 0 (negative) and 1 (abnormal)**
- **Presented to the operator as a quintiles 1-5 and 10 FOVs are available for scrutiny via GS Review Station**
- **Slides with a very high NPV are categorised as No Further Review (NFR). Can be sent straight to file as negative. No FOVs are available**

## RESEARCH HYPOTHESIS:

# CAN COMPUTER ASSISTED IMAGING ENHANCE QUALITY WITHIN THE SCREENING PROGRAMME FOR CERVICAL CANCER?


CAN COMPUTER ASSISTED IMAGING ENHANCE QUALITY WITHIN THE SCREENING PROGRAMME FOR CERVICAL CANCER?
Rapid QA screening
Comparison of Manual to Automated Primary Screening
NFR Reporting Category
Evaluation of Automated Detection of Endocervical Cells
Comparison of HPV ToC to FP GS
Economic Analysis
Screener Acceptance of the FP GS Technology

# Study Design

- **Prospective, multicentre randomised controlled trial to perform a Health Technology Assessment**
- **Planned to conform to CONSORT guidance for RCTs**
- **Designated CAESAR (Computer Assisted Evaluation, Screening And Reporting)**
- **Performed in 3 phases (CAESARs, 1,2 &3) involving 4 Welsh laboratories**
- **Samples were randomised by date of receipt and FocalPoint™ system availability (outside of project control)**
- **Ethical approval granted by LREC on 30.08.2008 – participant consent was not required (Health Technology Assessment)**
- **TOTAL of 45,317 samples were scanned by FocalPoint™ and 93,473 were screened manually**

# Study Logistics

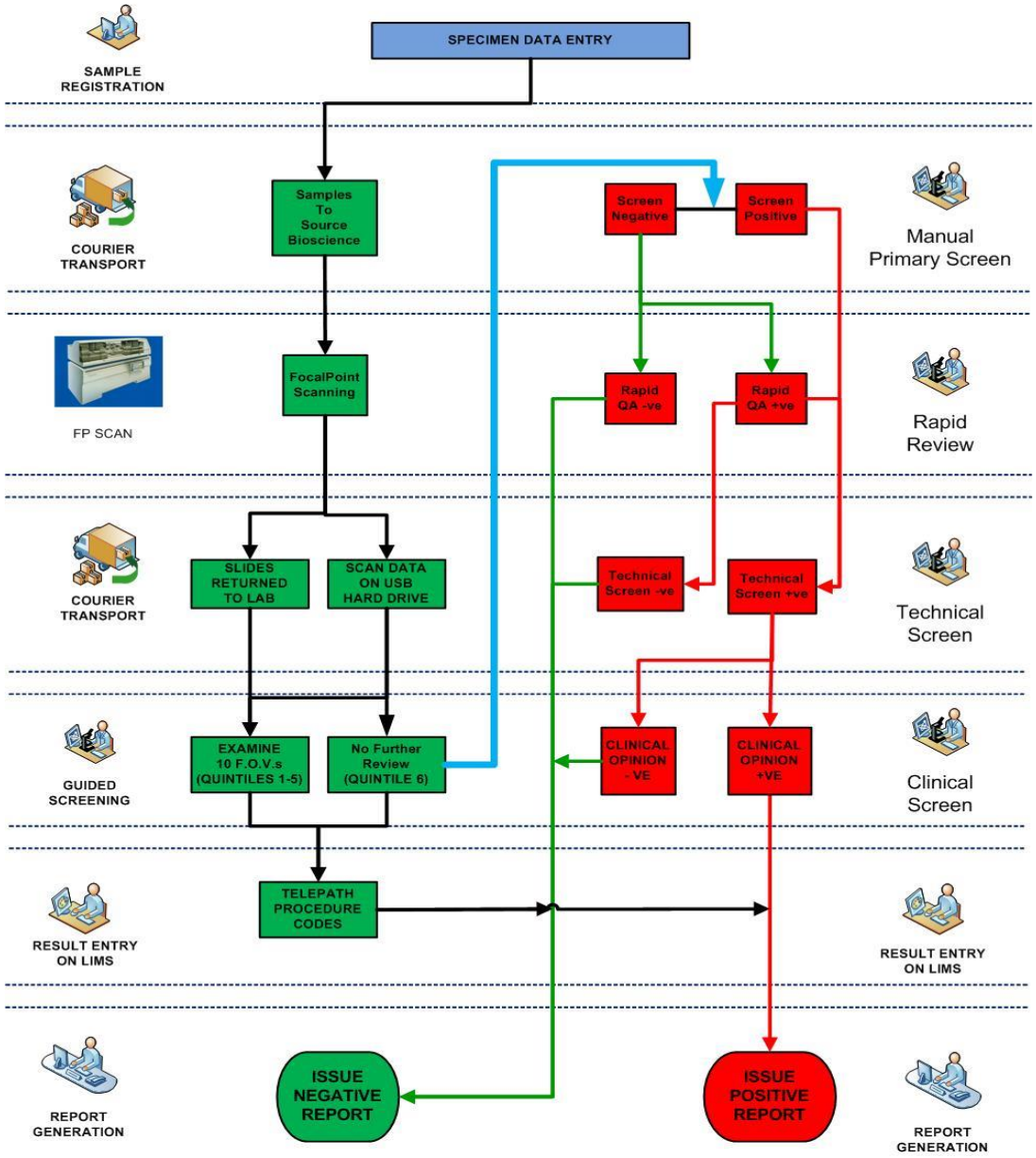
| Study | Start date | Finish date |
|---|---|---|
| **CAESAR 1** | December 14th, 2006 | December 6th, 2007 |
| **CAESAR 2** | July 1st, 2009 | May 31st, 2010 |
| **CAESAR 3** | December 1st, 2010 | July 31st, 2011 |

- **CAESAR 1**
- Three laboratories within North Wales participated in this initial study:
  - Glan Clwyd Hospital (GCH), situated near Rhyl
  - Llandudno General Hospital (LLGH)
  - Maelor General Hospital (WMH), Wrexham

- **CAESAR 2**
- For this study, a fourth additional laboratory was recruited
  - Royal Gwent Hospital (RGH), Newport

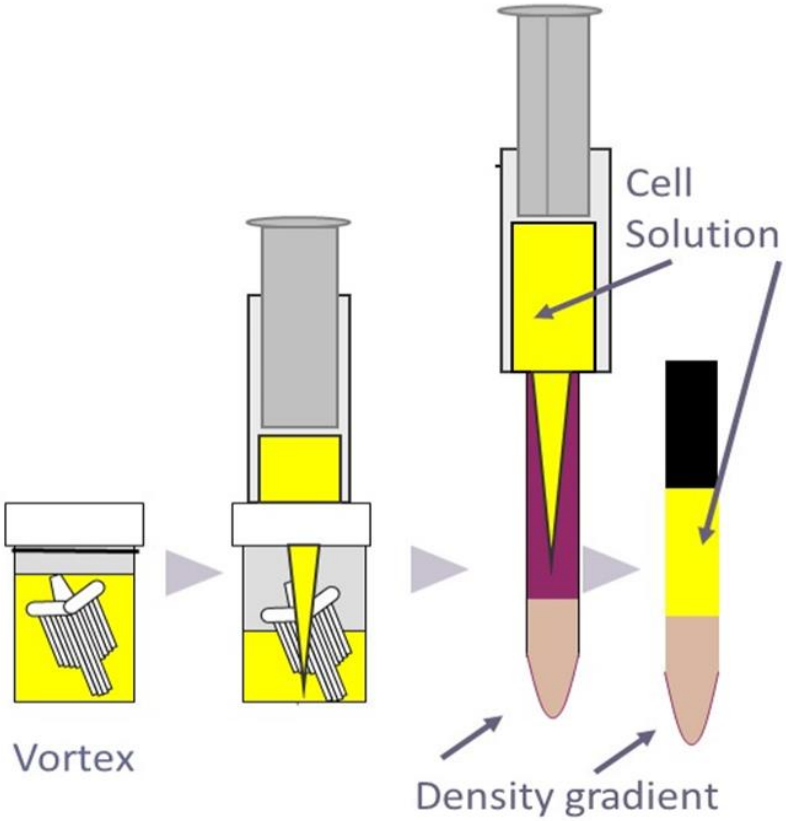
- **CAESAR 3**
- To further examine the reporting characteristics of the FocalPoint™ NFR category
- Due to staffing constraints and backlogs, only one laboratory (RGH) took part in this study

# CAESAR Sample Process Flow



# Sample Processing

## The SurePath™ PrepMate™



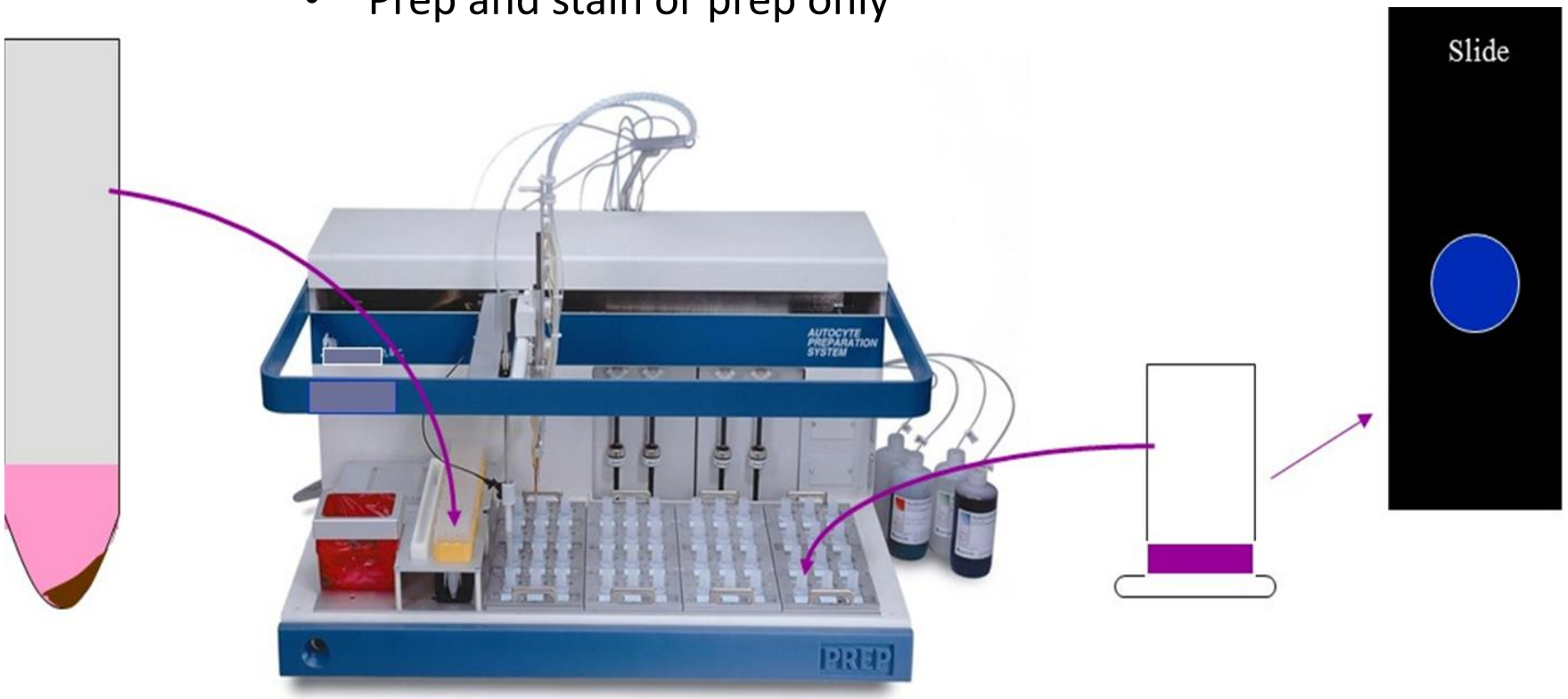


PREPMATE®

# Sample Processing

The SurePath™ AutoCyte Prep™

- Resuspend cell pellet
- Transfer to settling chamber
- Prep and stain or prep only



# FocalPoint™ Scanning Process

Slide Selection and Loading the instrument

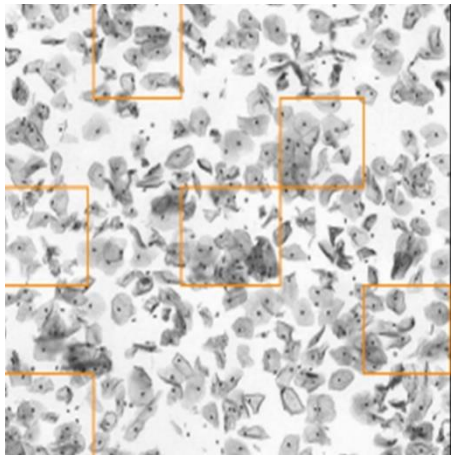
- **Add barcoded label to stained slide**

**LOAD and LEAVE**

- **Load slide trays into FocalPoint™ loading hopper**
- **Max 36 slide trays at any one time = 288 slides**
- **Minimum 120 slides per run**
- **No maximum limit of slides per run**

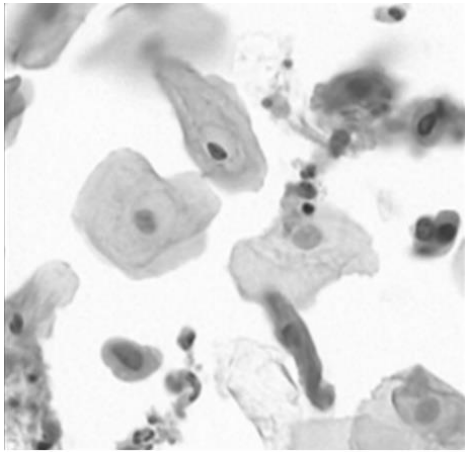
# BD FocalPoint™ Scanning Process

Low Power Scan



- **Slide scanned 3 times with x4 objective:**
  - Top to bottom; left to right and middle to periphery in a spiral fashion
- **Creates a 3D map of the entire cell deposition area**
- **Each x4 FOV is divided into 25 x20 sub-fields, and**
  - A SIL score (1 – 10) and GRP score (1 – 10) assigned
  - 1000 of the highest scoring x20 sub-fields will be analysed further

High Power Scan

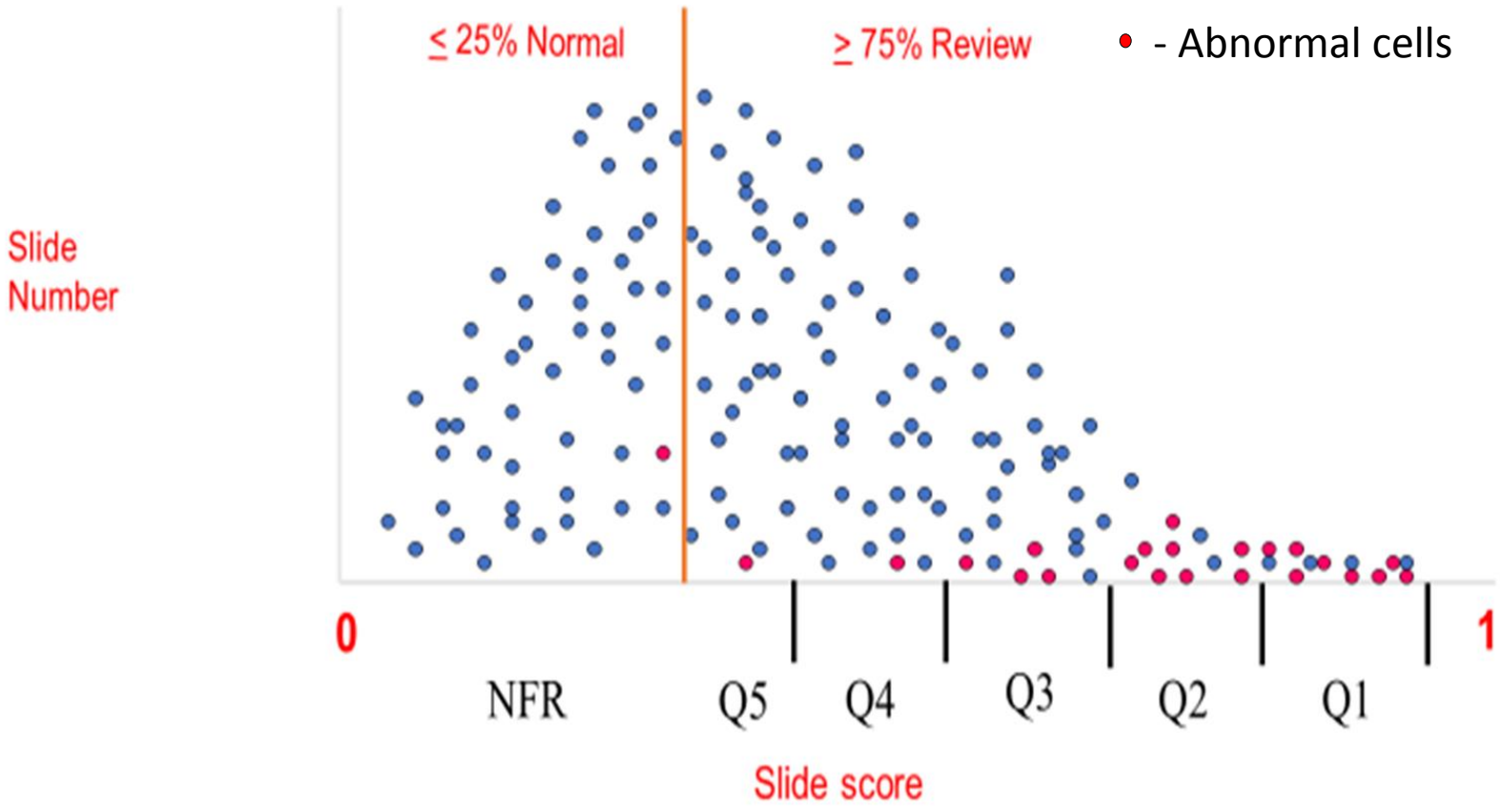


- **Each sub-field is scanned twice at x20 (high resolution)**
  - A high resolution image is acquired for every one of the 1000 Fields of View (FOVs)
- **FocalPoint's FoV processors separate all meaningful objects from the background**
  - These objects are classified as single cells, groups and thick groups
- **A cell, group and thick group score is assigned to each FOV and collated into an overall slide score of between 0 and 1**

# Qualified Slides – Sorting and Ranking

The BD FocalPoint™ SORTS and RANKS slides based on the likelihood of abnormality being present

0 = Negative, 1 = Abnormal.



# Data Collection and Analysis

**Data collection**

- **Bespoke code tables developed for the TelePath LIMS systems**
- **Data collected by established routine weekly data downloads to the Cervical Screening Wales data warehouse and collated for this study**

# Power Calculation

- **Calculated to detect differences in detection of high grade dyskaryosis (HSIL) at a prevalence of 1-2% of total samples screened**
- **Powered at 90% to detect a 4% difference in detection rates to a level of significance of 5%**
- **The calculation indicated that a minimum of 38,200 samples were needed**
- **The final total of samples scanned by the FocalPoint™ was 45, 317 – >twice the SurePath™ component of the MAVARIC trial**
- **Sample total high – deliberately so to allow for the proportion of NFR samples within this total (20-25%)**

# Statistical Tools used in the Evaluation

- **Chi-Squared test ($X^2$): as a test of association, and in combination with a *P* value to denote significance**
- **Confidence Interval (CI): these intervals have been calculated by use of bespoke software - Confidence Interval Analysis – version 2.0.5**
- **Tools used to compare the differences between 2 and 3-year interval outcomes of manual primary screening and the FocalPoint™ NFR reporting category**

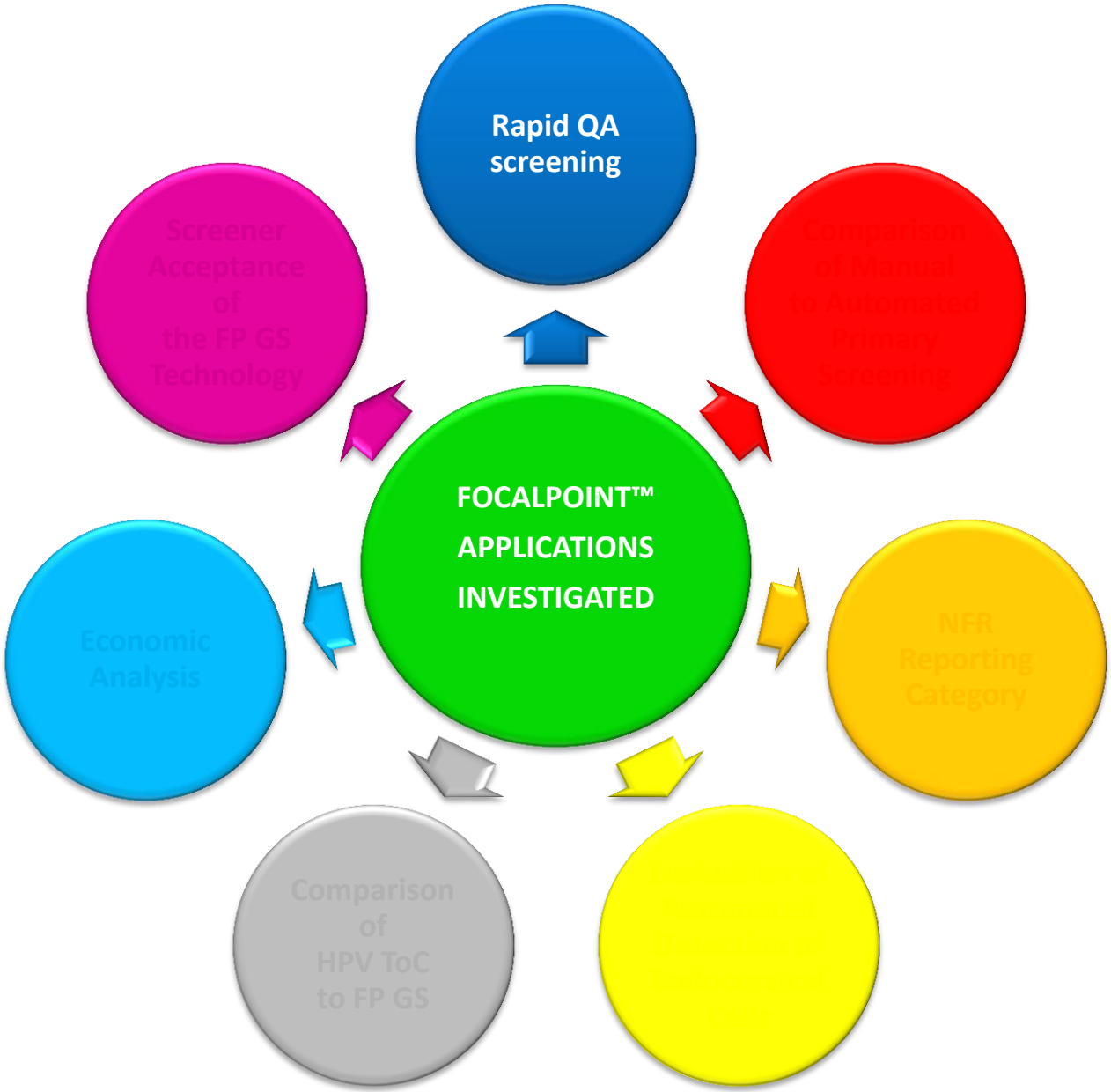
# Statistical Tools used in the Evaluation

- **Cohen's Kappa Statistic ($\mathcal{K}$)**

  Used to compare agreement of test results – specifically in the correlation between manual versus FocalPoint™ detection of endocervical cells

- **Cytology Key Performance Indicators (KPIs)**

- False Negative and False Positive rates
- Sensitivity
- Specificity
- Positive Predictive Value (PPV)
- **Difficult to calculate the absolute sensitivity for FocalPoint™ – because difficult to identify false negatives for both FocalPoint™ and manual screening – a relative sensitivity is used (Kitchener et al. 2011)**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# RAPID QA SCREENING

## Background and Methods

- **Currently method of choice for the Quality Assurance of Primary Screening in the UK and Ireland**
- **Cytotechnologist performs a rapid re-screen of the slide in a stepwise fashion**
- **Comparison of 10 FOV provided by FP LGS with manual Rapid QA screen**
- **Parameters for comparison:**
  - Time taken compared to manual Rapid QA screen
  - Comparison of screener sensitivities between CAS and manual rapid QA

# Rapid Quality Assurance Screening

## Comparison of Rapid QC times – Manual vs. Automated

Average time to examine 10 FOV (CAESAR 1)

| Laboratory | No. of Slides | Time Range from | (min:sec) to | Mean time (min:sec) |
|---|---|---|---|---|
| LLandudno | 5,747 | 00:02 | 18:03 | 01:26 |
| Wrexham | 3,336 | 00:03 | 22:58 | 01:26 |
| Glan Clwyd | 3,893 | 00:02 | 17:18 | 01:23 |
| Average | | | | **01:25** |

Average time to manually Rapid QC a slide (CAESAR 1)

| No. of Slides | Time Taken (mins) | Time/Slide (min:sec) |
|---|---|---|
| 2159 | 3596 | **01:38** |

**Summary: Rapid QC screen times using the FocalPoint™ Location Guided Screener (LGS) compare favourably with manual rapid rescreen**

# Rapid Quality Assurance Screening

## Comparison of Key Performance Indicators – Manual vs. Automated

**FocalPoint™LGS Rapid QA data vs. manual cytology final report:**

| | |
|---|---|
| Total of abnormal cases – all grades | 833 |
| Total of false negative cases – all grades | 260 |
| Sensitivity for high grade dyskaryosis | **90.14%** |
| Sensitivity for low grade dyskaryosis | **74.13%** |
| Sensitivity for all grades of dyskaryosis | **76.21%** |

**Manual rapid preview screen data vs. manual cytology final report:**

| | |
|---|---|
| Total of abnormal cases – all grades | 4720 |
| Total of false negative cases – all grades | 1672 |
| Sensitivity for high grade dyskaryosis | **85.58%** |
| Sensitivity for low grade dyskaryosis | **71.47%** |
| Sensitivity for all grades of dyskaryosis | **73.84%** |

**Summary of results: Sensitivity of LGS rapid QC screening is marginally improved compared to manual rapid preview**

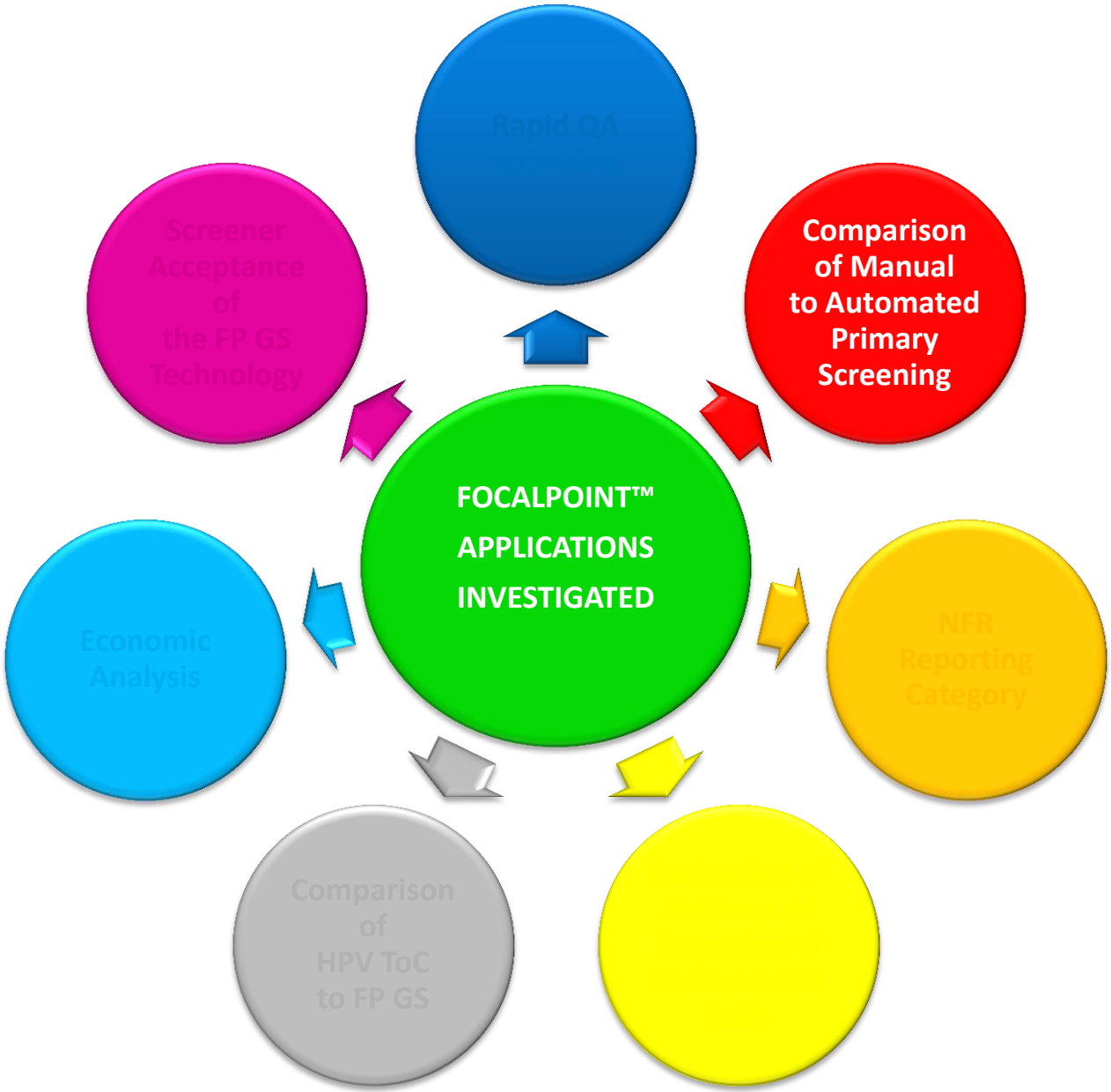
# Rapid Quality Assurance Screening

## Comparison of Key Performance Indicators(KPI) – other publications

| | | | Sensitivity | | |
|---|---|---|---|---|---|
| Study | Year | Total | Low | High | Average |
| Faraker et al. | 1996 | 9,517 | 82 | 91 | 86.5% |
| Brooke et al. HIGH GRADE | 2002 | 86,881 | 54 | 92 | 73% |
| Brooke et al. ALL GRADES | 2002 | 86,881 | 33 | 74 | 53.5% |
| Renshaw et al. | 1999 | | 38 | 89 | 63.5% |
| Tavares et al. | 2008 | 6,135 | 71.3 | 92.2 | 81.75% |
| Djemli et al. | 2006 | 8,364 | 15.4 | 72.7 | 44.05% |
| Patten et al. | 1997 | 14,914 | 52 | | 52% |
| CAESAR 2 automated HIGH GRADE | 2010 | 8,277 | | | 90.14% |
| CAESAR 2 automated LOW GRADE | 2010 | 8,277 | | | 74.13% |
| CAESAR 2 manual HIGH GRADE | 2010 | 48,268 | | | 85.58% |
| CAESAR 2 manual LOW GRADE | 2010 | 48,268 | | | 71.47% |

**Summary of results: Sensitivity of FocalPoint™ LGS rapid QC screening also exceeds manual rapid QC performance reported by other researchers**

**Conclusion: From this data, it is proposed that Rapid QC screening by FocalPoint™ LGS is a safe substitution for manual laboratory QC screening**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# MANUAL vs. AUTOMATED PRIMARY SCREENING

## Background and Methods

- **Due to the ongoing MAVARIC Study – directive from NHS CSP stating that no UK laboratory should use CAS for primary screening at that time**
- **Only option was to compare FocalPoint™ 10 FOV with Manual Primary screening**
- **Therefore the cytotechnologist was allowed to evaluate 10 FOV only, which disadvantaged the FocalPoint™ arm**
- **Parameters measured:**
  - False negative and false positive rates; low grade and high grade sensitivities of 10 FOVs presented compared with primary screening
  - Comparison of 3 year interval outcomes between Focal CAS and manual primary screening

# Manual vs Automated Primary Cytology Screening

**FP LGS vs. Manual Screening - comparison of outcomes at 2 and 3 years**

| Outcomes | LGS 10 FOV<br>Total samples = 19,655 | Samples manually screened to CSW SOPPs<br>Total Samples = 93,473 |
|---|---|---|
| CIN 2+(HSIL+) cases @ 2 years | **74** | **208** |
| Percentage (of total) @ 2 years | **0.386%**<br>(95% CI 0.27% to 0.48%) | **0.22%**<br>(95% CI 0.18% to 0.24%) |
| CIN 2+(HSIL+) cases @ 3 years | **105** | **366** |
| Percentage (of total) @ 3 years | **0.534%**<br>(95% CI 0.35% to 0.72%) | **0.39%**<br>(95% CI 0.35% to 0.43%) |

**Note: Incidence of CIN 2+ higher in FocalPoint™ LGS screened cohort at 2 and 3 years**

# Manual vs Automated Primary Cytology Screening

## Comparison of KPIs – FP LGS vs. National Standards

| | |
|---|---|
| **NHS CSP minimum sensitivity – high grade dyskaryosis** | **>95%** |
| **NHS CSP minimum sensitivity – all grades dyskaryosis** | **>90%** |
| **FocalPoint™ sensitivity of LGS 10 FOV – high grade dyskaryosis** | **= 90.14%** |
| **FocalPoint™ sensitivity of LGS 10 FOV – all grades dyskaryosis** | **= 76.21%** |

### Comparison of KPIs – FP LGS vs. Manual Screening

| | Sensitivity – HG Dyskaryosis | Sensitivity – All Grades dyskaryosis |
|---|---|---|
| Manual screening – All Laboratories | 98.49% | 87.12% |
| FocalPoint™ LGS – All Laboratories | 90.14% | 76.21% |

# Manual vs Automated Primary Cytology Screening

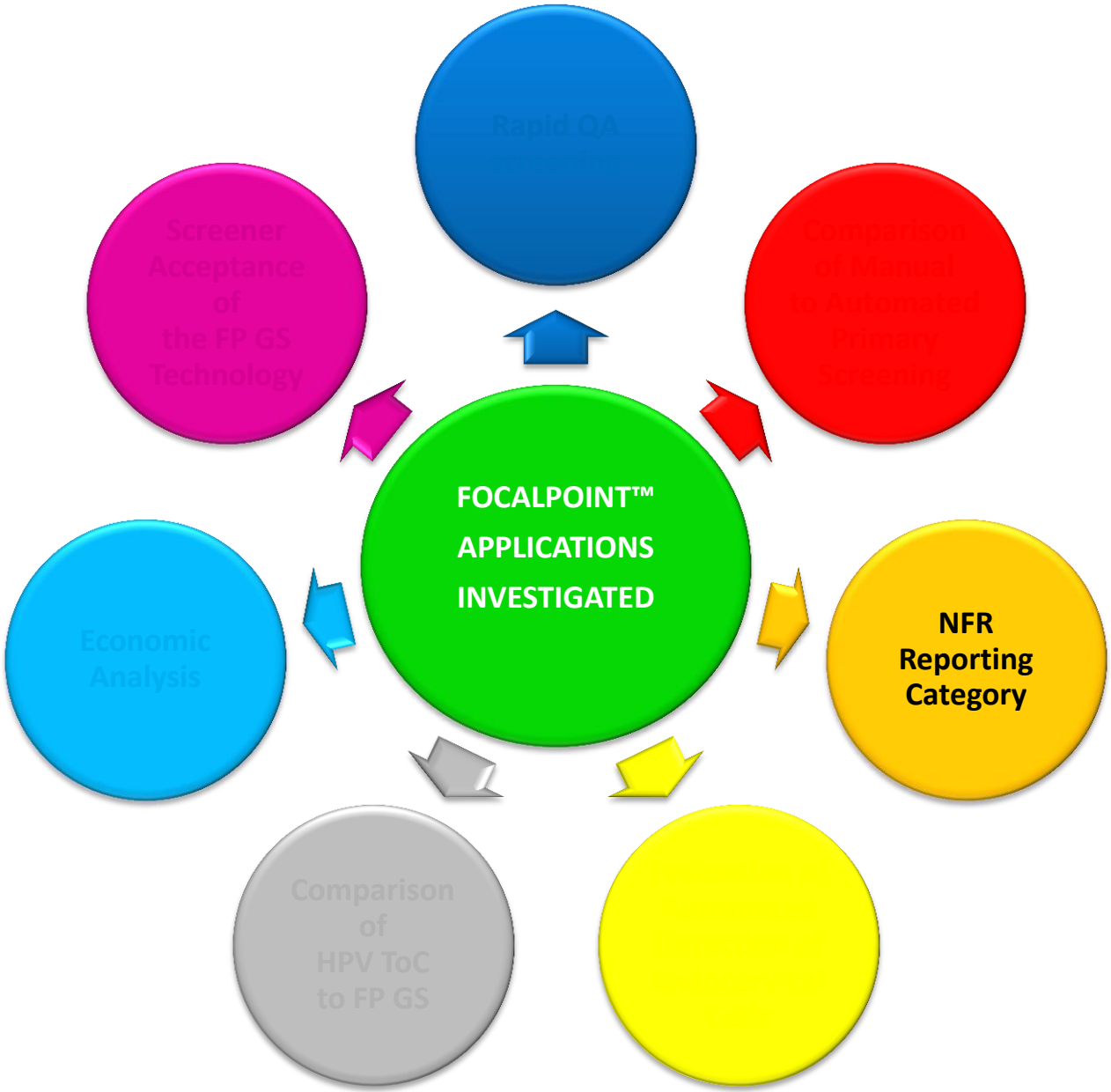
## Summary of results and conclusion

**Summary of results:**

- **Disease detection – interval disease outcome rates at 2 and years for manual primary screening exceed those of the FocalPoint™ cohort**
- **FocalPoint™ LGS is not as sensitive as manual primary screening for dyskaryosis and failed to reach minimum NHS CSP standards**

**Conclusion:**

- **The CAESAR results presented (minimalistic approach – 10 FOV only) indicate inferiority of CAS compared to manual primary screening**
- **This confirms the findings of the MAVARIC study**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# FOCALPOINT™ NO FURTHER REVIEW (NFR) REPORTING CATEGORY

## Background and Methods

- **No Further Review or NFR accounted for 20% of the total cases scanned in this study**
- **Slides allocated to NFR can theoretically be reported as 'negative' and placed directly to file**
- **Compared the 2 and 3 year interval outcomes of these cases compared to those of manually primary screened cases reported as *"negative, no dyskaryosis seen"***
- **Both the NFR designated cases and those manually reported as negative were submitted to manual rapid QC screening**

# FOCALPOINT™ NO FURTHER REVIEW (NFR) REPORTING CATEGORY

NFR vs. Manual Screening interval outcomes at 2 and 3 years

| Outcomes | FocalPoint™ NFR Total samples = 8,130 | Samples manually screened as per existing CSW SOPPs Total samples = 93,473 |
|---|---|---|
| CIN 2+(HSIL+) cases @ 2 years | **9** | **208** |
| Percentage (of total) @ 2 years | 0.11% (95% CI 0.05% to 0.21%) | 0.22% (95% CI 0.18% to 0.24%) |
| CIN 2+(HSIL+) cases @ 3 years | **19** | **366** |
| Percentage (of total) @ 3 years | 0.23% (95% CI 0.15% to 0.36%) | 0.39% (95% CI 0.35% to 0.43%) |

# FOCALPOINT™ NO FURTHER REVIEW (NFR) REPORTING CATEGORY

NFR vs. Manual Screening interval outcomes at 2 and 3 years

| | FocalPoint™ NFR Total samples = 8,130 | | Samples manually screened as per existing CSW SOPPs Total samples = 93,473 | |
|---|---|---|---|---|
| | Pre-cancers | Cancers | Pre-cancers | Cancers |
| **After 2 years** | **8** | **1** | **198** | **10** |
| **Percentage Of total – 2 years** | 0.098% * (95% CI 0.05% to 0.19%) | 0.012% (95% CI 0.002% to 0.07%) | 0.199% * (95% CI 0.17% to 0.23%) | 0.011% (95% CI 0.006% to 0.02%) |
| **After 3 years** | **17** | **2** | **345** | **21** |
| **Percentage Of total – 3 years** | 0.21% (95% CI 0.13% to 0.33%) | 0.025% (95% CI 0.07% to 0.09%) | 0.37% (95% CI 0.33% to 0.41%) | 0.022% (95% CI 0.015% to 0.034%) |

# FOCALPOINT™ NO FURTHER REVIEW (NFR) REPORTING CATEGORY

## Summary of results and conclusion

**Summary of results:**

- **HSIL+ interval cases at 2 and 3 years were increased in the manually screened cohort**
- **Precancer cases at 2 and 3 years were increased in the manually screened cohort**
- **Overlap in CI is reduced for 3 year interval data**
- **There was no significant difference in interval cancer cases (2 and 3) years between the two cohorts**

**Conclusion:**

- **NFR demonstrates non-inferiority to manual primary screening, with fewer CIN2+/HSIL+ and cervical precancer (CIN2/CIN3) (HSIL) cases presenting at 2 years**
- **The improvement is sustained and is even greater at 3 years**
- **NFR technology is a viable alternative to manual primary screening in a cervical screening programme**

# Unpredicted behaviour of the FocalPoint™ NFR technology

**During CAESAR 1, the NFR reporting category was entirely predictable**
**Only one case finally reported as high grade (severe) dyskaryosis**

| | Llandudno | Wrexham | Glan Clwyd | TOTAL |
|---|---|---|---|---|
| Inadequate | 6 | 0 | 5 | 11 |
| Negative | 1,242 | 695 | 816 | 2,753 |
| Borderline | 19 | 24 | 13 | 56 |
| Mild | 13 | 4 | 4 | 21 |
| Moderate | 0 | 0 | 0 | 0 |
| Severe | 1 | 0 | 0 | 1 |
| ? Invasive | 0 | 0 | 0 | 0 |
| ? Glandular | 0 | 0 | 0 | 0 |
| TOTAL | 1.281 | 723 | 838 | 2,842 |

# Unpredicted behaviour of the FocalPoint™ NFR technology

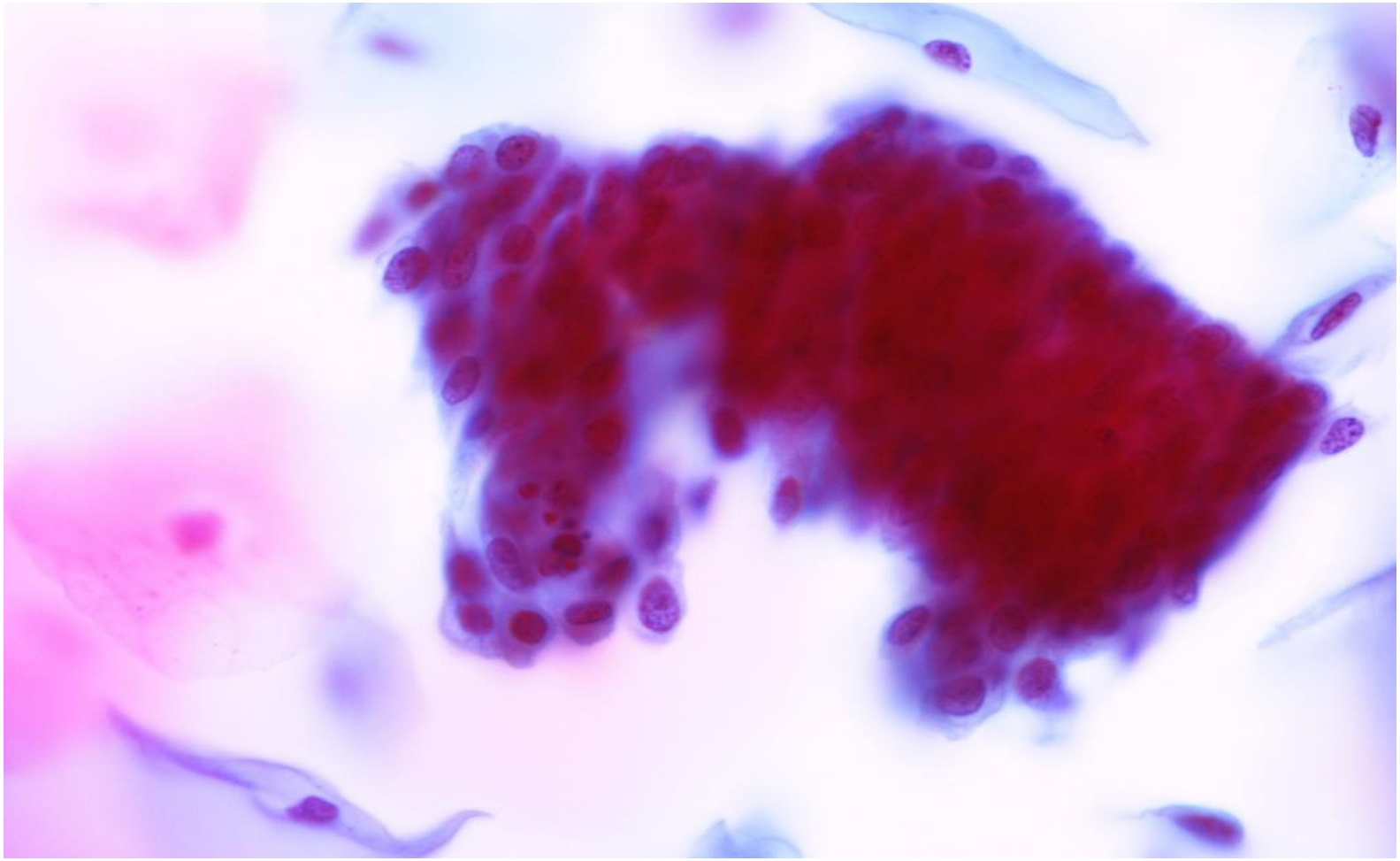
**During CAESAR 2, several occurrences of cases assigned to NFR were finally reported as high grade dyskaryosis (11 cases in 9 runs)**

| Laboratory | Run No. | Cytology Result | Histology result |
|---|---|---|---|
| Llandudno | 9 | BNA/?HG | CIN3 |
| | 43 | Severe Dyskaryosis | CIN3 |
| | 43 | BNA/?HG | CIN3 |
| | 43 | Severe Dyskaryosis | CIN3 |
| | 47 | Severe Dyskaryosis | CIN3 |
| | 60 | AGUS & Mod [6H,7] | CIN2 |
| | 60 | Moderate Dyskaryosis | CIN3 |
| | 65 | Severe Dyskaryosis | CIN3 |
| | 24 | Severe Dyskaryosis | CIN 1 |
| Royal Gwent | 15 | Moderate Dyskaryosis | N/A |
| | 27 | Moderate Dyskaryosis | CIN2 |

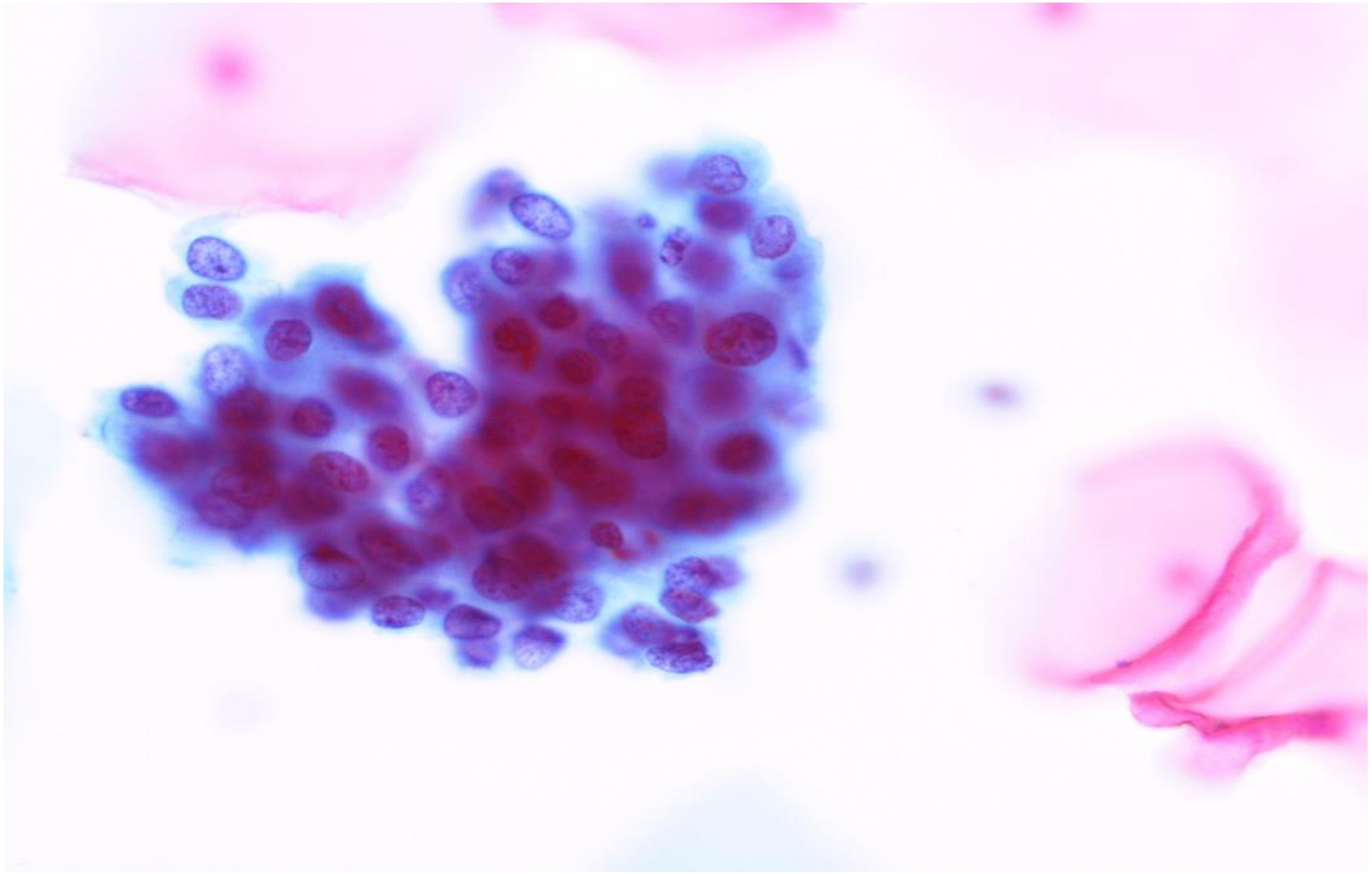
# Unpredicted behaviour of the FocalPoint™ NFR technology

- **The level of incidence of High Grade samples assigned to NFR during December and January 2009-10 was unprecedented**
- **Several orders of magnitude greater than during CAESAR 1**
- **Incidence rate for CAESAR 1 was 1/2842, in this instance as high as 2/3 cases in a single run!**
- **Confidence in the NFR technology severely undermined**
- **Source Bioscience contacted, and several conference calls between CSW, Source Bioscience, Becton Dickinson**
- **Slides affected were reviewed and photographed and anonymised images shared with the manufacturer**
- **The typical morphological features of the affected slides were:**
  - Dense microbiopsies with steep edge relief, featuring anisonucleosis
  - Dyskaryotic small squamous cells often seen in severe dyskaryosis (HSIL)
  - Single “litigation” type small dyskaryotic cells

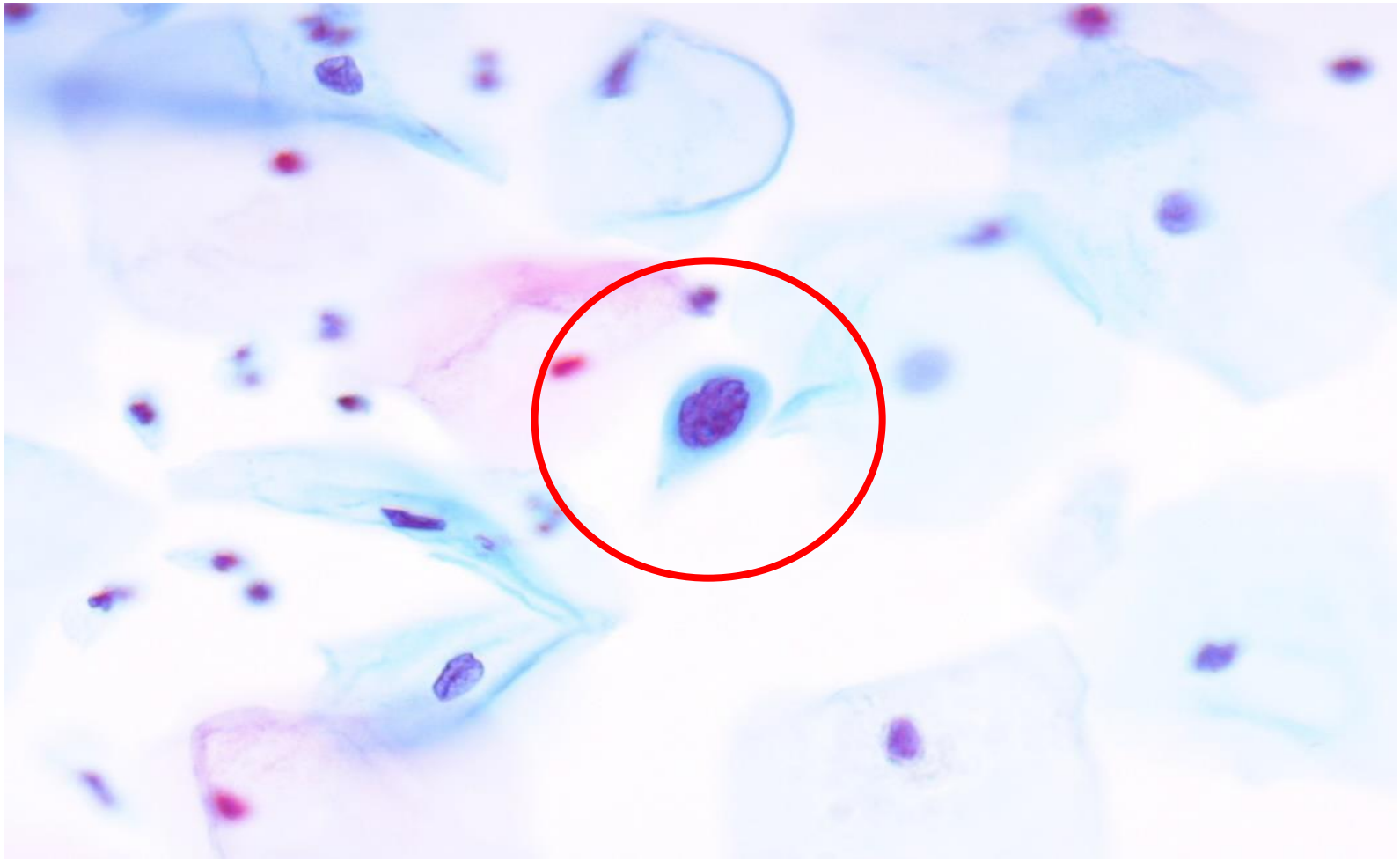
# Unpredicted behaviour of the FocalPoint™ NFR technology



# Unpredicted behaviour of the FocalPoint™ NFR technology



# Unpredicted behaviour of the FocalPoint™ NFR technology



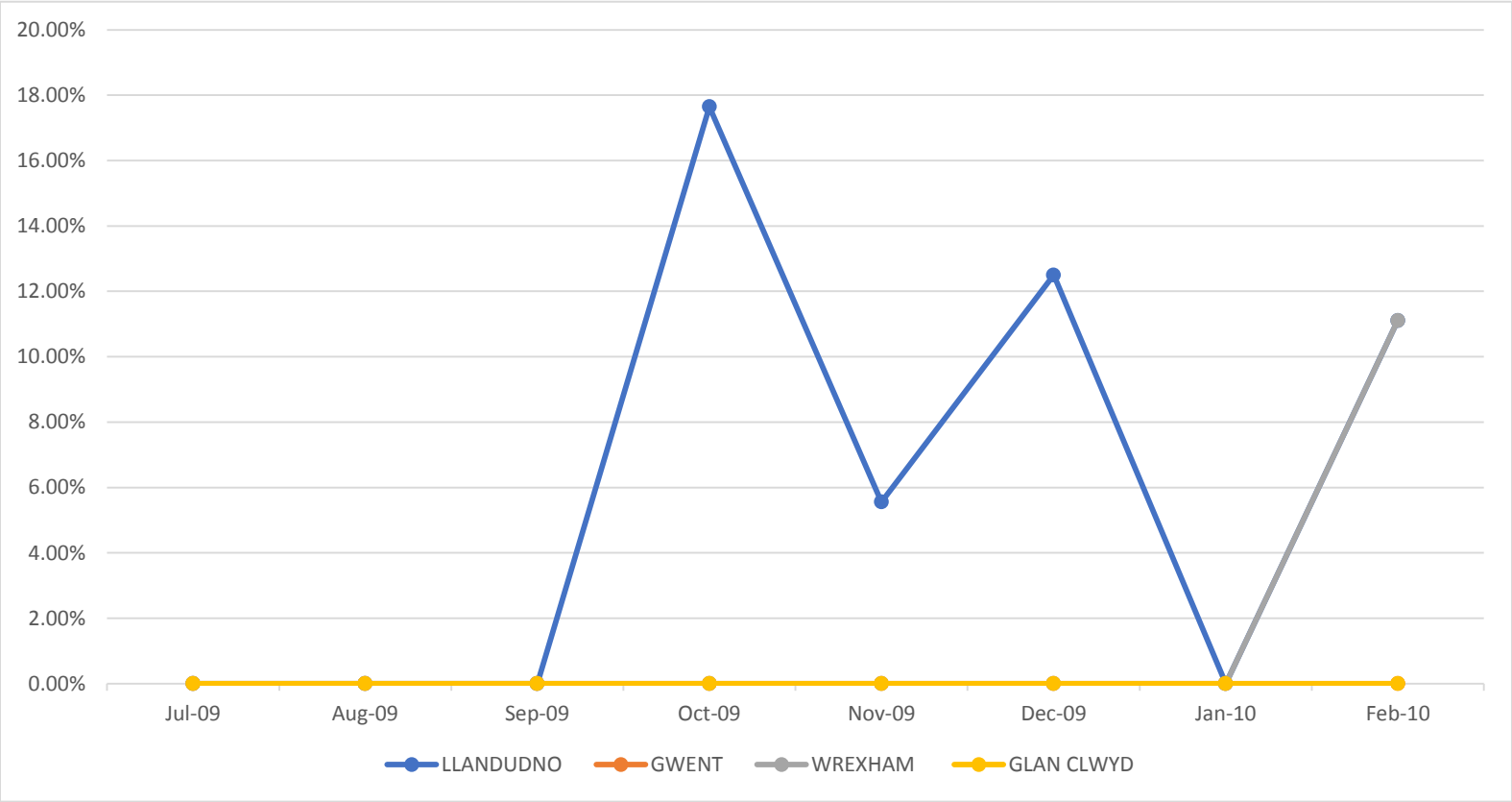
# Unpredicted behaviour of the FocalPoint™ NFR technology

## Outcomes of the Investigation

- **Investigation concluded that the FocalPoint™ GS instrument was functioning according to specification**
- **The Laboratory Process Calibration Assessment (LPCA) had been carried out by initial scanning of 250 cases as per current protocol**
- **This calibration served all 4 laboratories – no further calibration was carried out**
- **As part of the investigation the batches of slides concerned were re-scanned with NFR threshold set to 0. This resulted in abnormal cells presenting to the cytotechnologist in FOVs**
- **16, 932 samples scanned in CAESAR 2 to date were investigated further, with particular references to outcomes**

# Unpredicted behaviour of the FocalPoint™ NFR technology

Outcomes of the investigation

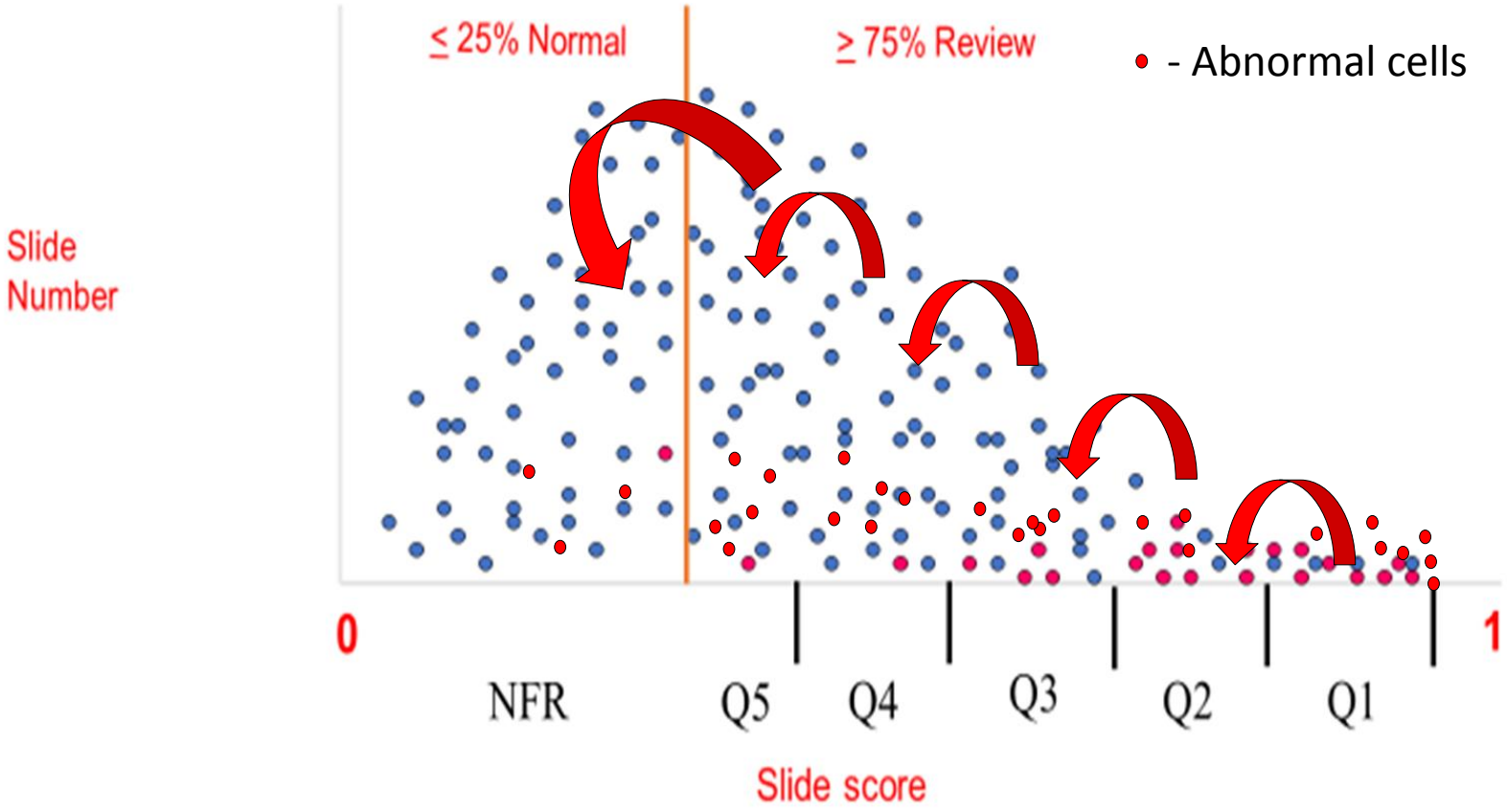



- When the threshold of expected prevalence rates is set to 0%, it is evident that the Llandudno and Wrexham laboratories experienced greater than usual levels high grade disease

# The Algorithm Super–Saturation effect

Increased prevalence of abnormality over that expected from calibration will cause a cascade effect that will challenge the system

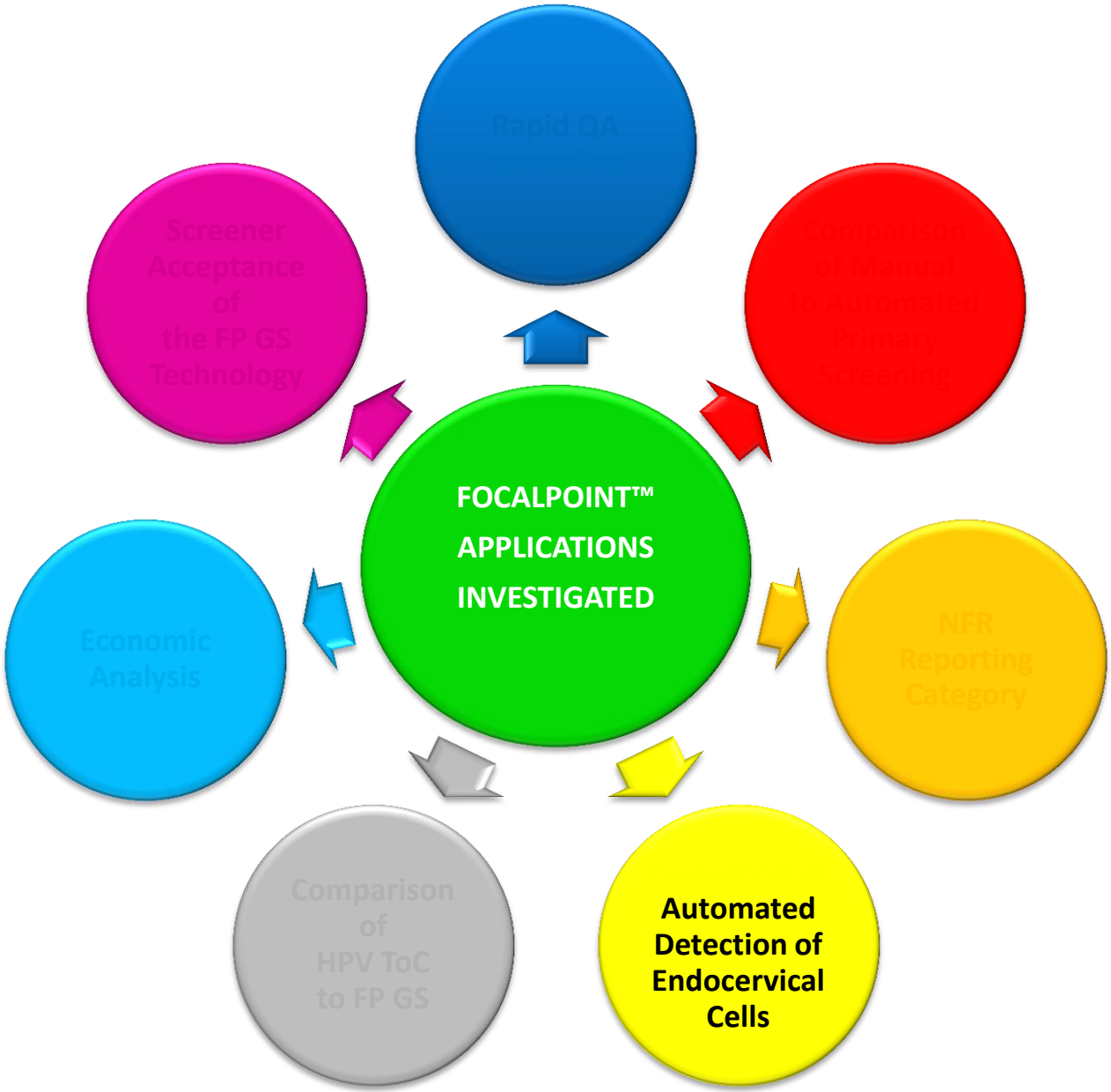
0 = Negative, 1 = Abnormal.



# Unpredicted behaviour of the FocalPoint™ NFR technology

## Outcome, Summary and Conclusion

- **The phenomenon is thought to be the result of an "Algorithm Super-saturation effect"**
- **BD responded with a revised protocol for LPCA calibration**
- **Initial scan now 1000 slides, with continuous calibration checks against required parameters and feedback to users**
- **System calibration to manufacturer's recommendations is pivotal to maintaining accuracy and precision of results**
- **Important to maintain screening programme confidence and reputation**
- **Rapid QC screen is recommended as a means of ensuring process integrity**
- **This finding brought about a change in the manufacturer's calibration protocol that undoubtedly improved screening outcomes for numerous women in the UK and elsewhere**


Rapid QA Turnaround
Comparison of Manual to Automated Primary Screening
NFR Reporting Category
Automated Detection of Endocervical Cells
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FOCALPOINT™ APPLICATIONS INVESTIGATED

# EVALUATION OF THE AUTOMATED DETECTION OF ENDOCERVICAL CELLS

## Background and Methods

- **Cervical Transformation Zone (TZ) sampling is important for the optimal detection of cervical pre-cancer**
- **TZ detection is a useful "soft" indicator of sample taker performance, especially for trainee sample takers**
- **Conventionally, recorded during primary screening but NFR samples only have a rapid QA screen**
- **The FocalPoint™ has the capability to detect the presence or absence of the endocervical component of a cervical sample**
- **Compare the consistency of the FP results compared to manual Transformation Zone recording across 4 participating labs**
- **Study the degree of correlation of endocervical cell detection between the two technologies**
- **To ascertain if this functionality was a viable substitute for manual endocervical cell detection**

# EVALUATION OF THE AUTOMATED DETECTION OF ENDOCERVICAL CELLS

Manual TZ reporting versus FocalPoint endocervical component reporting rates

| Laboratory | Manual TZ Reporting Rates <50 | Focal Point Endocervical Component Detection Rates |
|---|---|---|
| Glan Clwyd | 81.0 | 84.7 |
| Llandudno | 96.5 | 81.5 |
| Wrexham | 85.4 | 78.4 |
| Average | 87.6 | 81.5 |
| S.D. | **8.0** | **3.1** |

# EVALUATION OF THE AUTOMATED DETECTION OF ENDOCERVICAL CELLS

Correlation between FocalPoint™ endocervical component and manual detection of endocervical cells

| FocalPoint™ +ve | Manual +ve | Total | Comments |
|---|---|---|---|
| **Yes** | Yes | 184 | Concordant |
| **No** | No | 36 | Concordant |
| **No** | Yes | 33 | Discordant |
| **Yes** | No | 29 | Discordant |
| **Insufficient cells** | No | 2 | Disqualified |
| | **TOTAL** | **284** | |

**Cohen's Kappa Statistic is 0.78 – indicating good agreement**

# EVALUATION OF THE AUTOMATED DETECTION OF ENDOCERVICAL CELLS

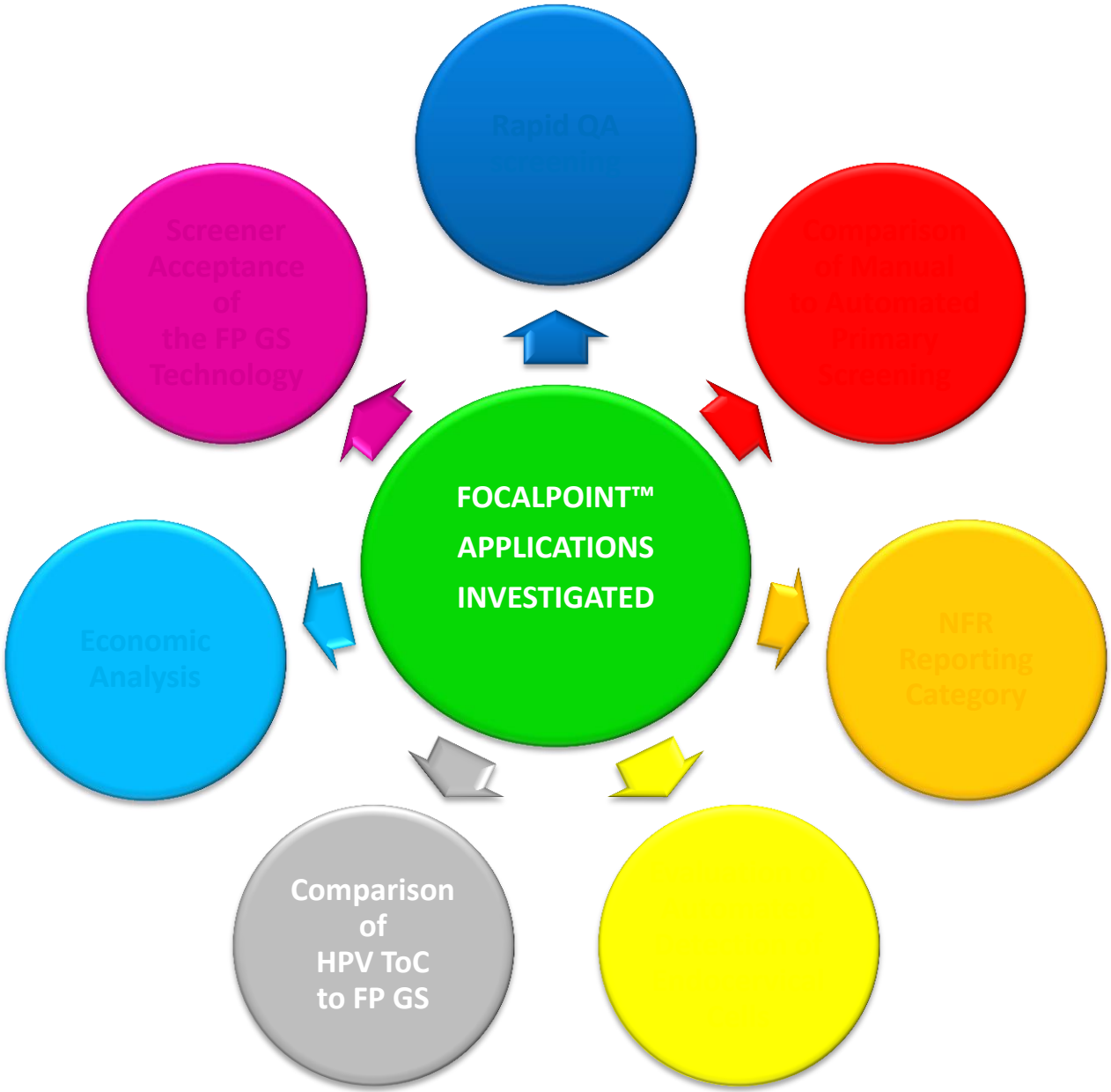
## Summary and conclusion

**Summary of results:**

- **FocalPoint™ endocervical cell component reporting range = 78.4 – 84.7%, SD = 3.1**
- **Manual TZ component reporting range = 81.0 – 96.5%, SD = 8.0**
- **FocalPoint™ / Manual endocervical cell detection concordance: Cohen's Kappa statistic ($\mathcal{K}$ = 0.78) – good agreement**

**Conclusion:**

- **Automated endocervical component detection is a viable alternative to manual TZ component detection in a cervical screening program**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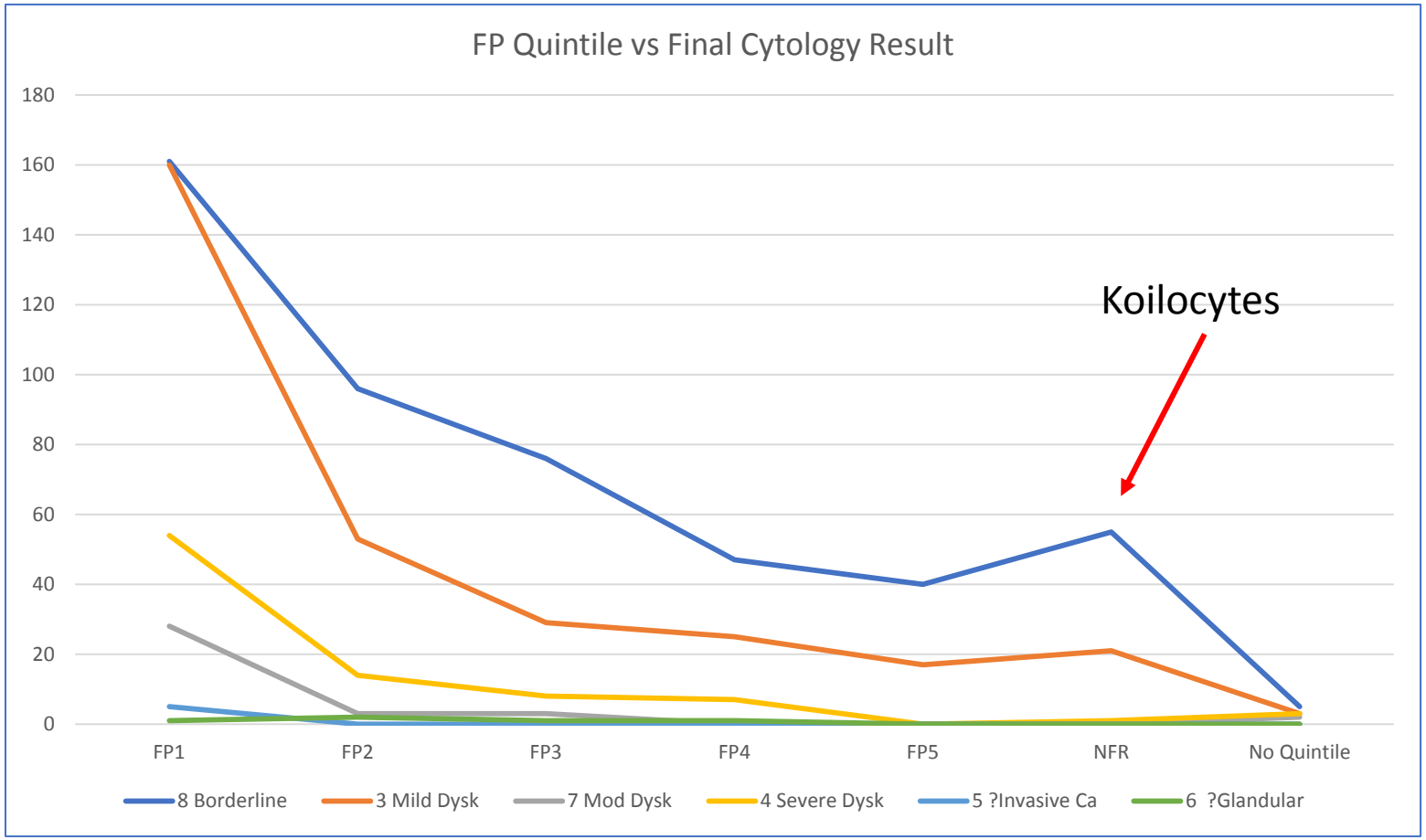
# Comparison of HPV ToC to FP GS

Relationship between FocalPoint™ and cytology result

- **Cervical Screening Wales introduced HPV testing in Test of Cure modality for treatment of CIN during the latter stages of this project**
- **A total of 128 HPV positive samples also had a FocalPoint™ quintile result**
- **The technology is designed so that the samples with highest abnormal potential are assigned to Quintile 1, then Quintile 2 and so on**
- **Decision to examine the relationship between FocalPoint™ Quintile and sample HPV status**

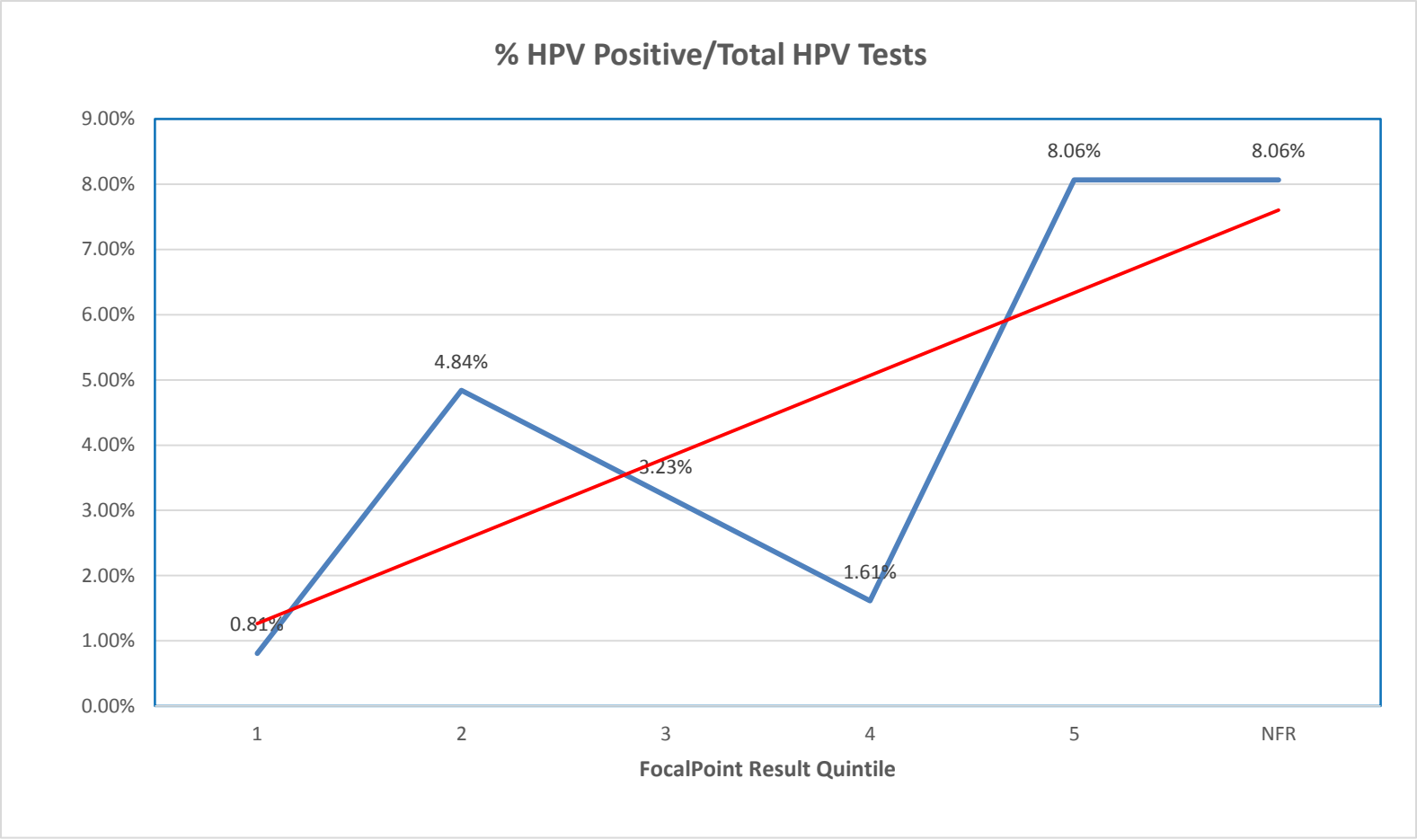
# Comparison of HPV ToC to FP GS

Relationship between FocalPoint™ and cytology result

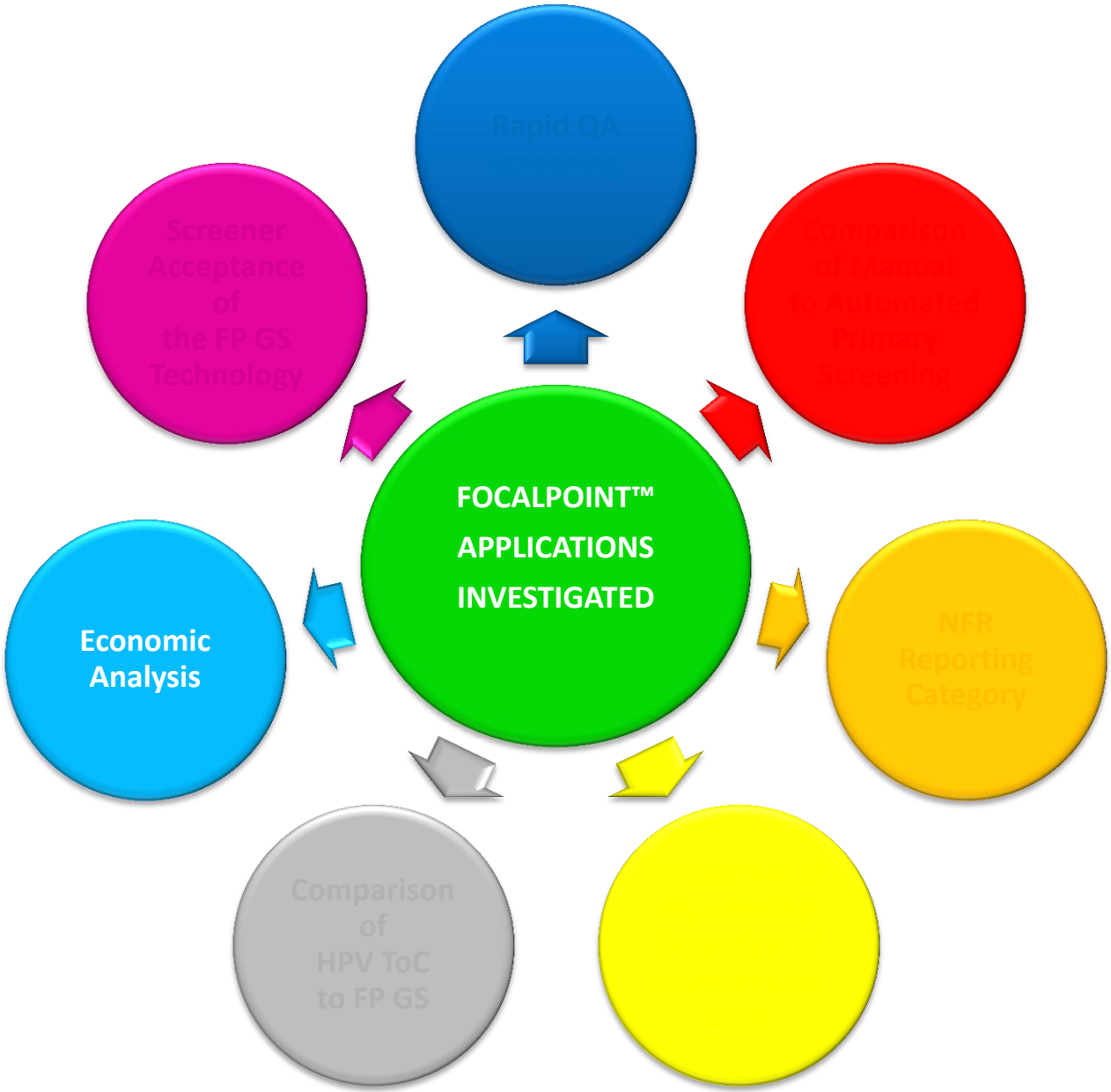


# Comparison of HPV ToC to FP GS

Relationship between FocalPoint™ Quintile and HPV ToC result




**Summary of results: HPV ToC positivity increase with FocalPoint™ Quintile, Including quintile 6 (NFR). Exception here is Quintile 4**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# ECONOMIC ANALYSIS

## Background and methods

- **Evident that some cost generating events common to both manual and automated processes**
- **Ascertained that these common processes had the same costs irrespective of pathway**
- **Identified cost generating events specific to each pathway – manual vs automated**
- **The analysis approach taken compared the costs of each cost generating event unique to each pathway**
- **This practice of excluding common costs to two interventions is accepted practice in health economic analysis as described by Drummond et al, 2015**
- **Quality a prime criteria in this evaluation – if a FocalPoint™ application was demonstrably inferior to the manual equivalent, then it was not considered in the EA**

# ECONOMIC ANALYSIS

## Background, methods and assumptions

- **From the results presented elsewhere in this thesis, the FocalPoint™ technology demonstrated non-inferiority in the following functions:**
  - Rapid Internal QC
  - Primary cytology screening using the FocalPoint™ NFR technology

- **The modelling exercises were based on following costs and assumptions:**
  - Cervical Screening Wales laboratory screening throughput during 2013-14
  - Agenda for Change (A4C) pay scales for laboratory staff
  - Samples rejected (Process Review or PRV) by the FocalPoint™ - reported as 4% of scanned samples during the project
  - NFR reporting rate of 21.8% of the samples during the project
  - Medical/CBMS staffing rates were excluded – clinical reporting processes and costs were the same for both automated and manual arms
  - FocalPoint™ Managed Service Contract costs - £420,000 per annum
  - Maximum of 5 hours per day screening
  - Minimum of 3,000 samples per annum – 5,000 per annum per w.t.e.

# ECONOMIC ANALYSIS

## Summary of results

- **Calculated costs – manual screening**
  - Projected cost of manually screening CSW workload (2013-14) =£1,352,758
  - Staffing costs in Wales (2013-14) =£933,828
  - CSW annual total workload =219,750 (220,000)
  - Total annual output (capacity) of samples screened by this model =147,250
  - Number of samples screened during overtime = 72,500
  - Cost of overtime to screen 72,500 samples =£628,395
  - Total cost for manual screening, including overtime =£1,562,223
- **Calculated costs - FocalPoint™ (NFR and LGS Rapid QC screen)**
  - Manual costs saved by NFR (46042 samples, time only) =£291,906
  - Manual costs saved by NFR (46042 samples, via overtime) =£399,184
  - Labour saving by using LGS rapid QC screen (time only) =£12,875

# ECONOMIC ANALYSIS

## Summary of results and conclusions

- **Calculated cost savings of implementing FocalPoint™ NFR and LGS rapid QC screen:**
  - FocalPoint NFR and LGS screen, time only (£291,906.28 + £12,873.92) =£304,780
  - FocalPoint NFR and LGS screen, overtime (£399,184.14 + £12,873.92) =£412,058

- **Cost of implementing FocalPoint™ NFR and LGS rapid QC screen:**
  - Costs of implementation (2013-14) amounted to =£420,000
  - No expectation of any net savings – even with overtime
  - However, if increased overtime working was anticipated in a backlog situation, there would come a point when the technology would create a saving
  - In recent years, recruiting qualified cytotechnologists has been difficult
  - In several UK laboratories screening could not have continued without NFR technology implementation


Rapid QA Screening
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FOCALPOINT™ APPLICATIONS INVESTIGATED

# Screener acceptance of the FocalPoint™ GS technology

## Background and methods

- **Screener perceptions of the CAS technology were recorded by a questionnaire and evaluated**
- **Qualitative evaluation included:**
    - Staff grade and length of service
    - Length of time operating FocalPoint™
    - Experience of the training and how it might be improved
    - Levels of acceptance of the technology
    - Challenges experienced
    - Were there any positive or adverse effects on implementation/operation in the workplace

# Screener acceptance of the FocalPoint™ GS technology

## Results and conclusion

- **14 questionnaires issued, 7 returned, 50% response rate**
- **Staff were happy with the manufacturer's training and assessment of competence**
- **Most staff accepted the technology and enjoyed using it**
- **2 staff stated that they preferred manual screening**
- **Same 2 staff found concentration harder with the LGS**
- **3 respondents found using the LGS challenging**
- **Most accepted that the LGS technology was not as monotonous as manual screening**
- **No respondents reported any discomfort or ill-effects using the technology**

# Screener acceptance of the FocalPoint™ GS technology

## Conclusion and discussion

- **Anecdotally, however, some staff did not appear to trust the technology**
- **Prolonged the rapid QC process per slide – almost to the point where it was another primary screen**
- **This may have had a negative impact on the overall throughput of the technology and**
- **Potentially – the potential labour saving benefits of the technology**

# Future directions

## The advent of HPV testing

- **One of the most important developments in cervical screening is the proven association between high-risk human papillomavirus and cervical disease**
- **The high NPP of a negative HPV test (NPV of 99.7%, Kitchener et al. 2009) is good news for the woman, BUT**
- **Positive result is not so clear, for a number of reasons:**
  - Persistence of infection
  - Immunocompetency of the woman
  - Integration of the virus with the woman's genome
  - HPV sub-type
- **In summary – A HPV test is a <u>test of risk, not a test of disease</u>**
- **So, what to do with those women who are HPV positive?**

# Future directions

## What about a sustainable "Test for Disease"?

- **Current thinking is to use cervical cytology as a reflex test to HPV**
  - This is not without problems as this SWOT analysis shows:
- **Strengths**
  - NHS Pathology services are changing (NHS Improvement plans, 2017)
  - A networking approach (as for Wales and to an extent, Scotland) is possible, but planning is "behind the curve"
  - Research into new, alternative tests is progressing, including:
    - Biochemical analyses such as RAMAN spectroscopy
    - Immunocytochemical biomarkers
    - Computer Assisted Screening
    - Combination of CAS used in the detection of biomarkers may well have further potential

# Future directions

## What about a sustainable "Test for Disease"?

- **Weaknesses**
  - Staffing challenges already referred to earlier
  - Uncertainties around disease prevalence in a HPV primary scenario
  - Managing small numbers for reflex testing – staff competencies
  - Maintaining sustainable cytology services
- **Opportunities**
  - Urgently investigate alternative technologies
  - Re-structure training for cytologists?
- **Threats**
  - Declining cytology
  - Service reorganisation from Pathology services and laboratory screening tendering will have an impact – damage limitation

# Conclusions

## The future for CAS?

- **Study shows that there is and will continue to be a role for CAS in a cytology primary screening scenario**
- **FocalPoint™ may also have value as a reflex test technology, for increased disease prevalence population (Schiffman et al. 2017)**
  - Can be used to scan different LBC platforms
  - Operating algorithms adapted to compensate for increased level of abnormality prevalent in a HPV positive population
  - Go back to its roots – combine morphological detection algorithms with those for biomarker reaction end-point detection
  - Potential for more consistent application than the manual intervention
  - Development of operational detection thresholds that are clinically significant for patient management and reduce intra-operator variation?
  - Risk stratification and appropriate follow-up pathways?

# Publications and Presentations

## Publications

- **Published:**
  - Cuscheri K, Denton K, Nuttall D, Sargent A. Laboratory quality control and assurance for human papillomavirus testing. January 2017. Public Health England. NHS Cervical Screening Programme. www.gov.uk – accessed June 1, 2017
  - Hibbitts S, Tristram A, Beer H, McRea J, Rose B, Hauke A, Nuttall D, Dallimore N, Newcombe RG, Fiander A. UK population based study to predict impact of HPV vaccination. 2014. Journal of Clinical Virology. Feb;59(2):109-114
  - Denton K, Nuttall D, Cropper A, Desai M. Implementation of 'No Further Review' (NFR) using the BD FocalPointTM Slide Profiler. 2013. NHS Cervical Screening Programme: Good Practice Guide No. 4
- **Submitted for publication:**
  - Nuttall DS, Fox R, Hillier S, Dallimore N, Clayton H, Martin C, O'Leary JJ, Sloan S, Savage A. A Retrospective Validation of the Becton Dickinson Focal Point GS Slide Profiler NFR Technology by Analysis of Interval Disease Outcomes Compared to Manual Cytology Screening

# Publications and Presentations

## Publications

- **In preparation:**
  - Nuttall DS, O'Leary JJ, Martin C. The Effect of Variation in Screening Population on the FocalPoint™ Point GS No Further Review Technology: 'The Algorithm Super-saturation and Quintile Cascade Effect'

# Publications and Presentations

## Presentations

- **2016:**
  - European Congress of Cytology, 40th Conference. Liverpool. Oral Presentation: Improved Detection of CIN 2+ Lesions by the Becton Dickinson Focal Point™ GS Slide Profiler No Further Review Technology Compared to Routine Manual Slide Reading: An analysis of interval outcomes"
  - United States and Canadian Association of Pathology (USCAP) Annual Scientific Meeting. Seattle, USA. Oral Presentation: Improved Detection of CIN 2+ Lesions by the Becton Dickinson Focal Point™ GS Slide Profiler No Further Review Technology Compared to Routine Manual Slide Reading: An analysis of interval outcomes
- **2014:**
  - Cervical Screening Wales 15th Anniversary Conference – Cardiff. Oral Presentation: Cervical Screening Laboratory Services – the next 15 years!
- **2013:**
  - Update course for Consultant Biomedical Scientists East Pennine Cytology Training School. Oral Presentation: Cervical Screening Wales – A Different Perspective"
  - Cervical Screening Wales Colposcopy Conference – Llandrindod Wells. Oral Presentation: Introduction and Clinical Management of HPV Testing

# Acknowledgements


- **Professor John O'Leary**
- **Assistant Professor Cara Martin**
- **Dr James O'Mahony**
- **Colleagues working within the CERVIVA research consortium**
- **Cervical Screening Wales for supporting my research**
- **Laboratory Staff in Wales**
- **BAC and BD for support in attending USCAP**

- **Last but not least…….!**

**My wife, Enid and my family – caru chi oll!**

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

# Thank You