Gloucestershire Hospitals NHS
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The dynamics of HR HPV testing and vaccination in the Gloucestershire cervical screening programme

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Today's talk

- Introduction
- History of Gloucestershire lab – cytology and HR HPV testing
- The first 3 years – HC2
- The elephant in the room
- Reprocurement of HR HPV testing - Aptima
- Performance
- Effects on screening programme
- Conclusion

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History of lab – 1 Cytology

Cytology

- 1990 – Cheltenham – 18,000 from East Glos
- 2002 – GHNHSFT – 47,000 from Gloucestershire
- 2007 – Worcestershire programme added (39000) – total 86,000, Thin Prep LBC conversion
- 2012 – Herefordshire programme added (10,000) – total 85,000

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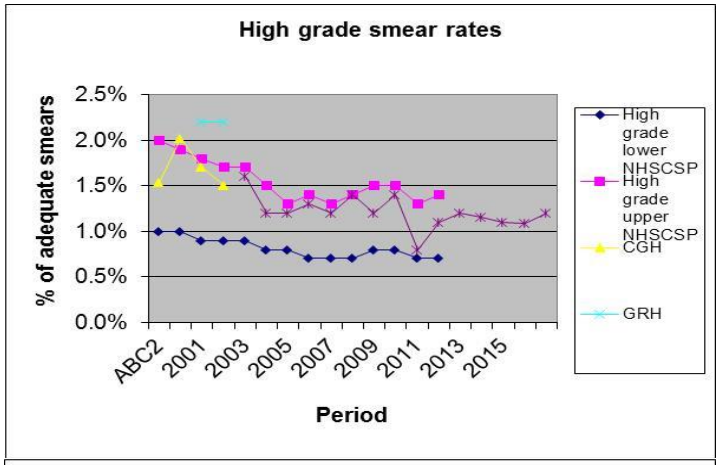
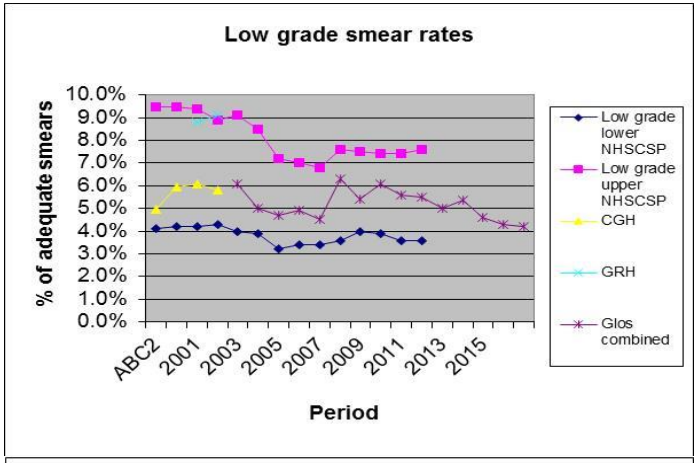
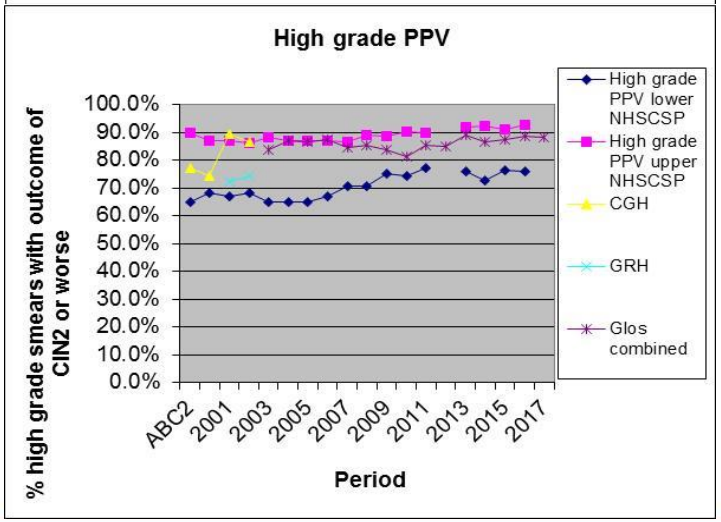
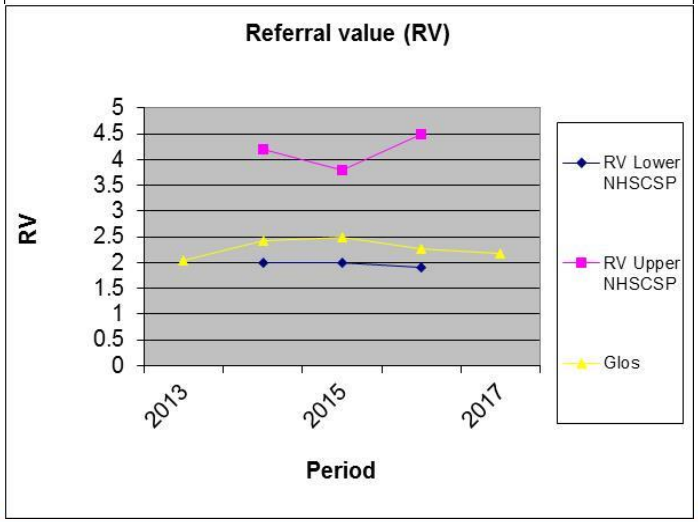
History of lab 2
Cytology reporting profiles









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Introduction of HR HPV testing – 2012 Systems originally mandated by NHSCSP

Supplier	Technology	Gloucestershire/external factors in 2012
Roche	DNA PCR	Platform available on GRH site – reported high positive rates
Abbott	DNA PCR	No local platform
Genprobe	RNA TMA	No local platform, infrastructure uncertain, high cost
Hologic	Cervista	New technology, no local platform
QIAGEN	HC2	No local platform, lent well to preferred local service model, cost effective, most data available.

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Introduction of HR HPV testing NHSCSP pathways

HPV testing

- Prior to 2012 – PCR HPV sub typing of difficult colposcopy management cases sent to TDL
- 2012 -13 NHS CSP Year 1 – New Test of Cure and Triage, HC2
- 2013-14 NHS CSP Year 2 – As year 1 plus catch up cohorts, HC2
- 2014-15 NHS CSP Year 3 – As year 2 plus TOC for CGIN, HC2

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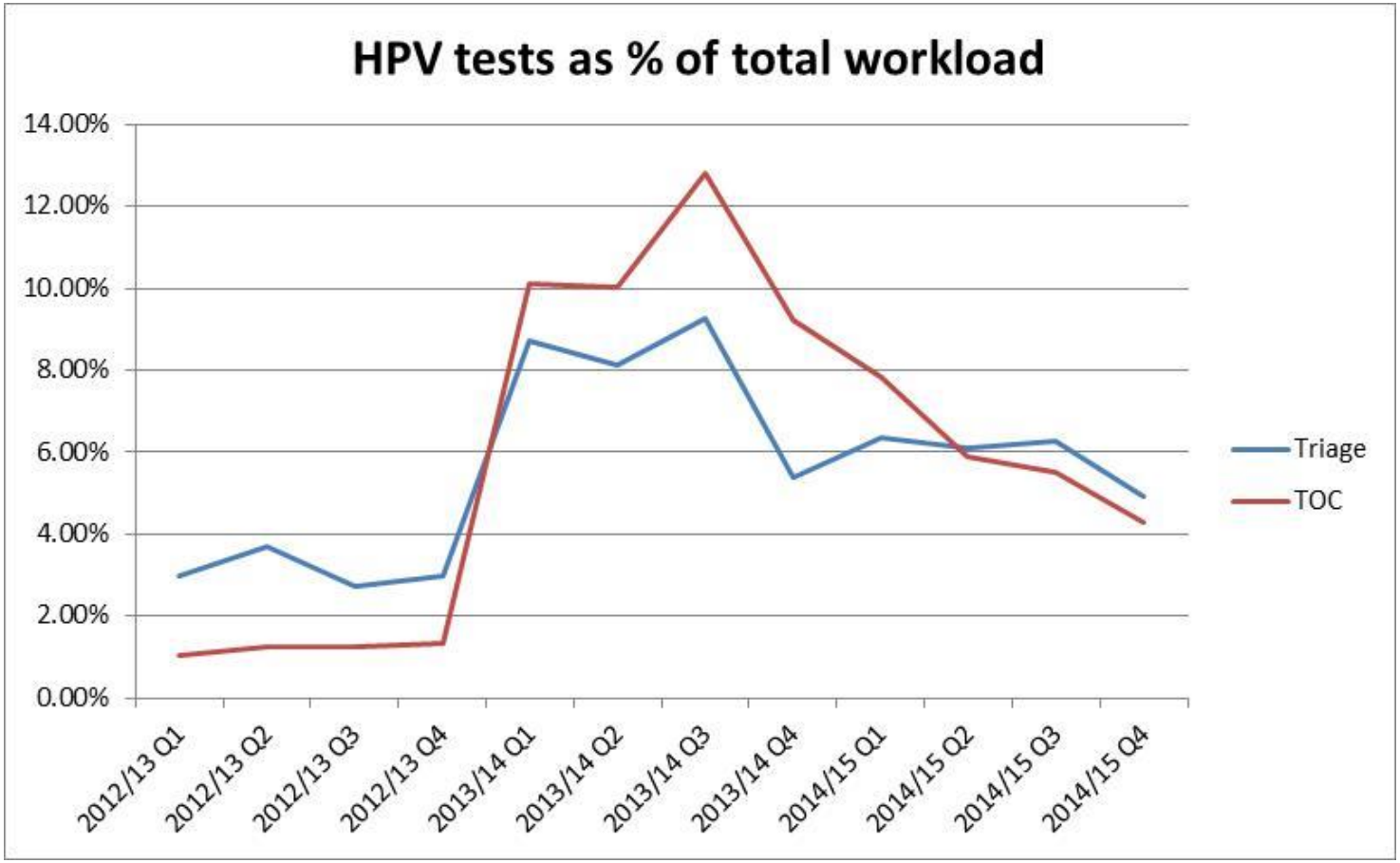
The first 3 years - HC2 – HR HPV test volumes



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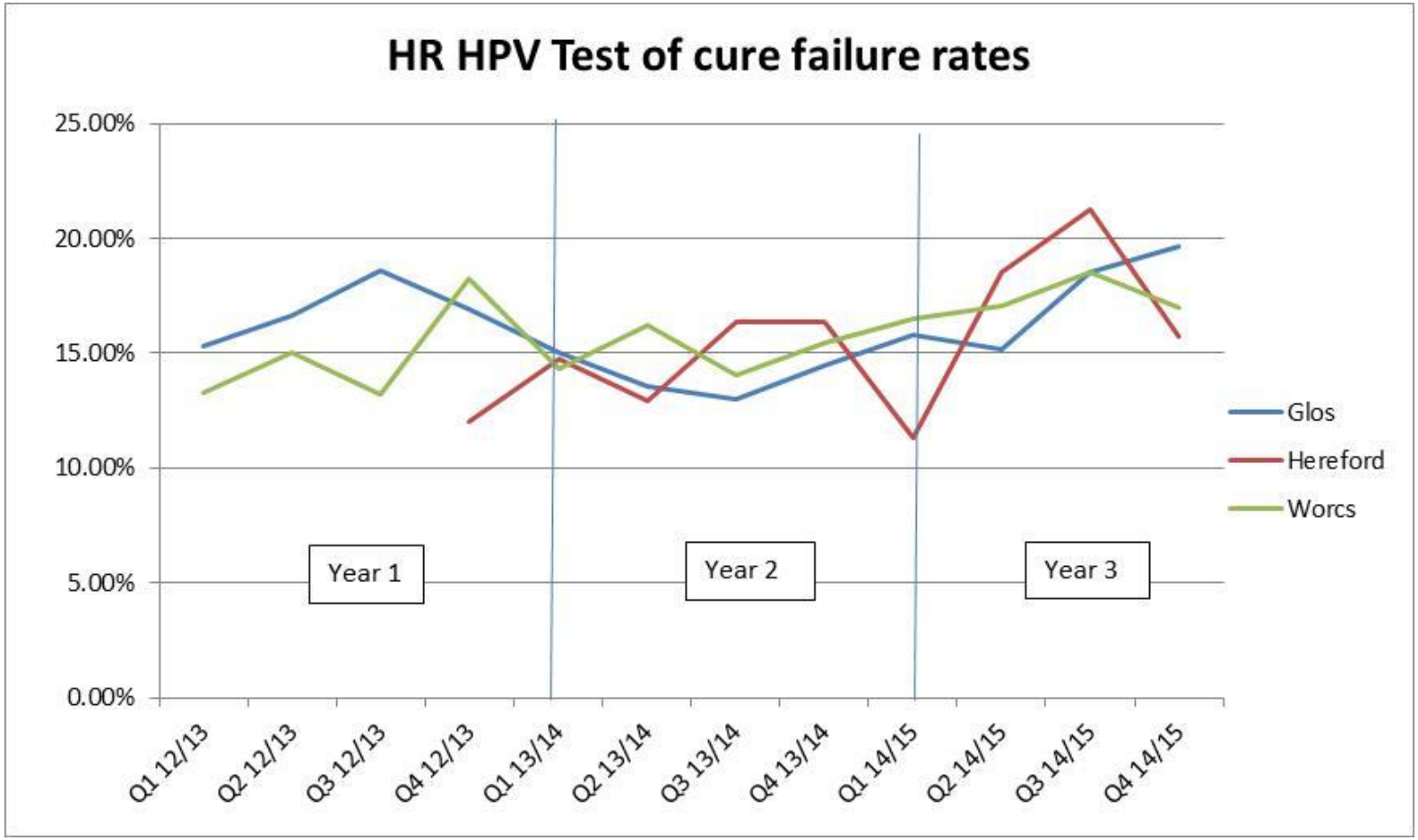
The first 3 years – HC2 - HR HPV results



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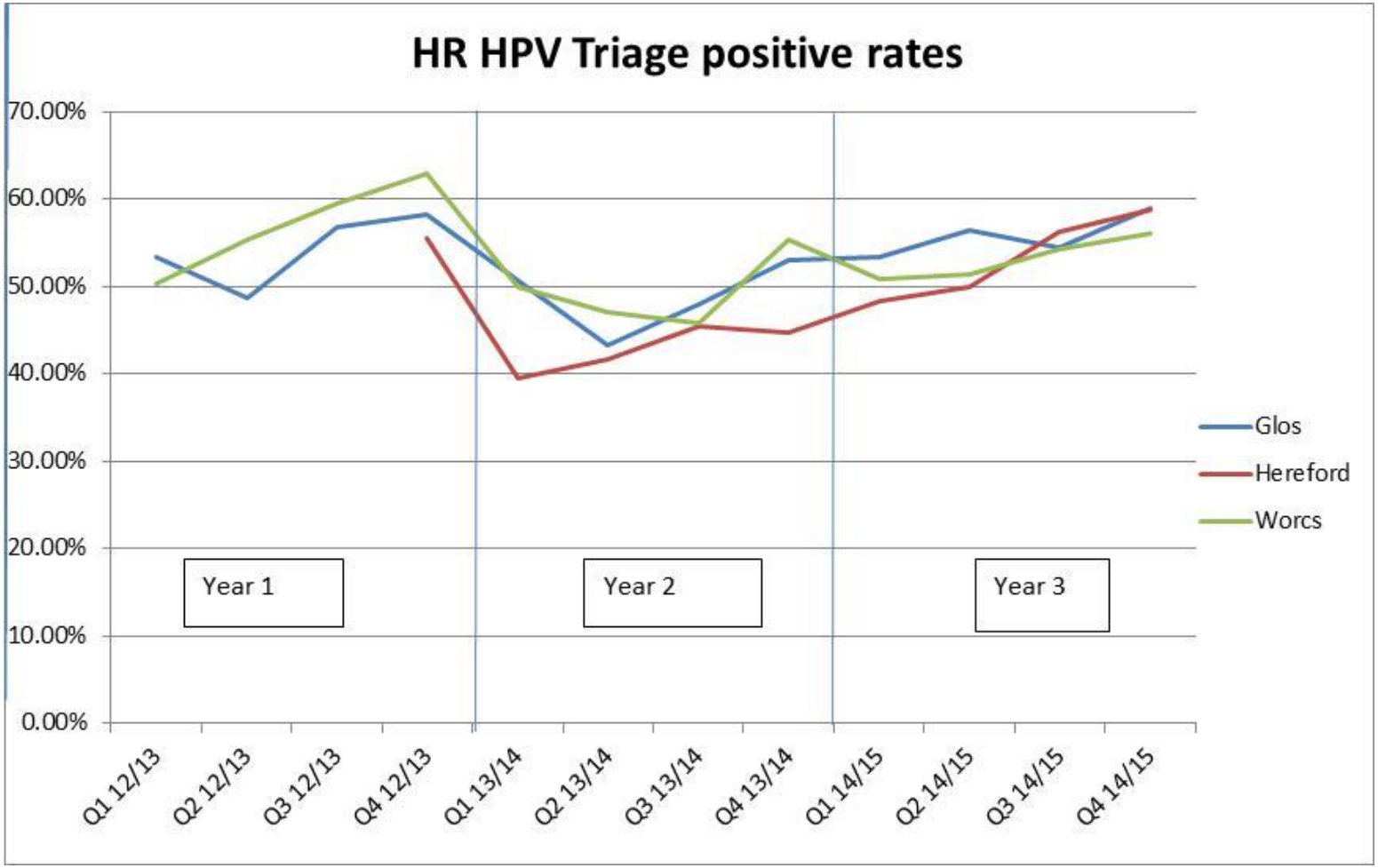
The first 3 years – HC2 - HR HPV results



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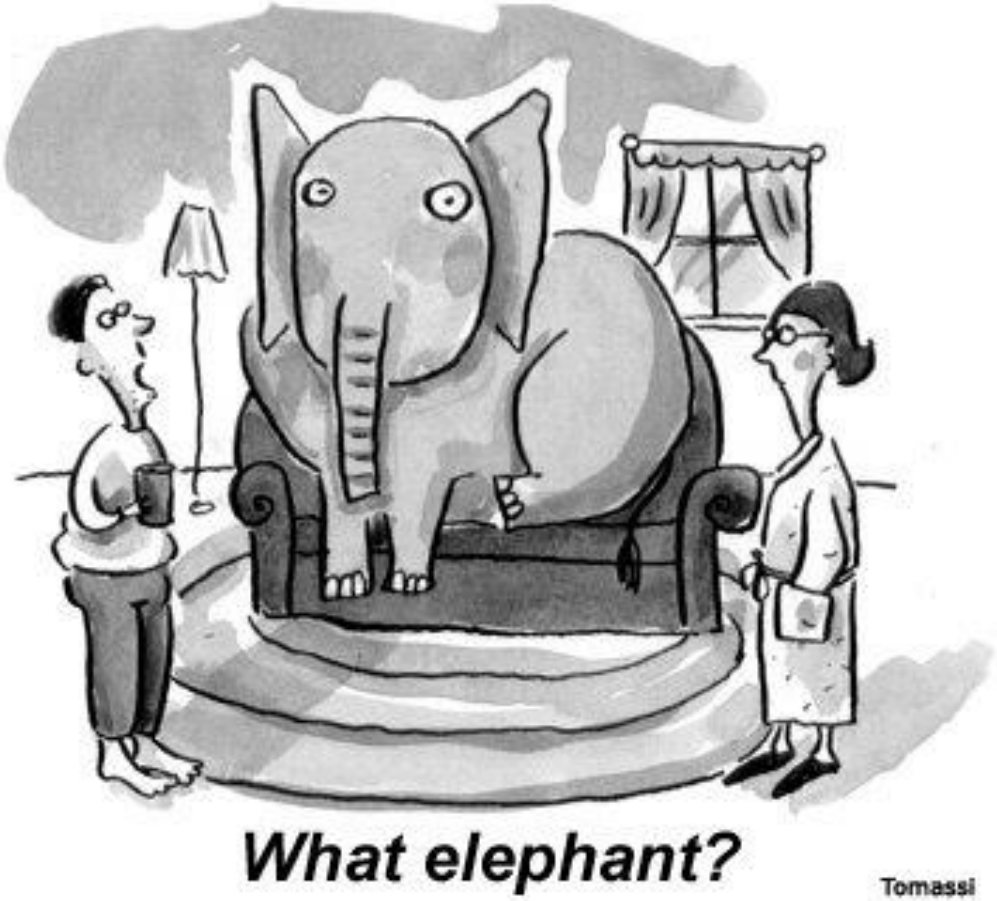
HPV testing - The elephant in the room



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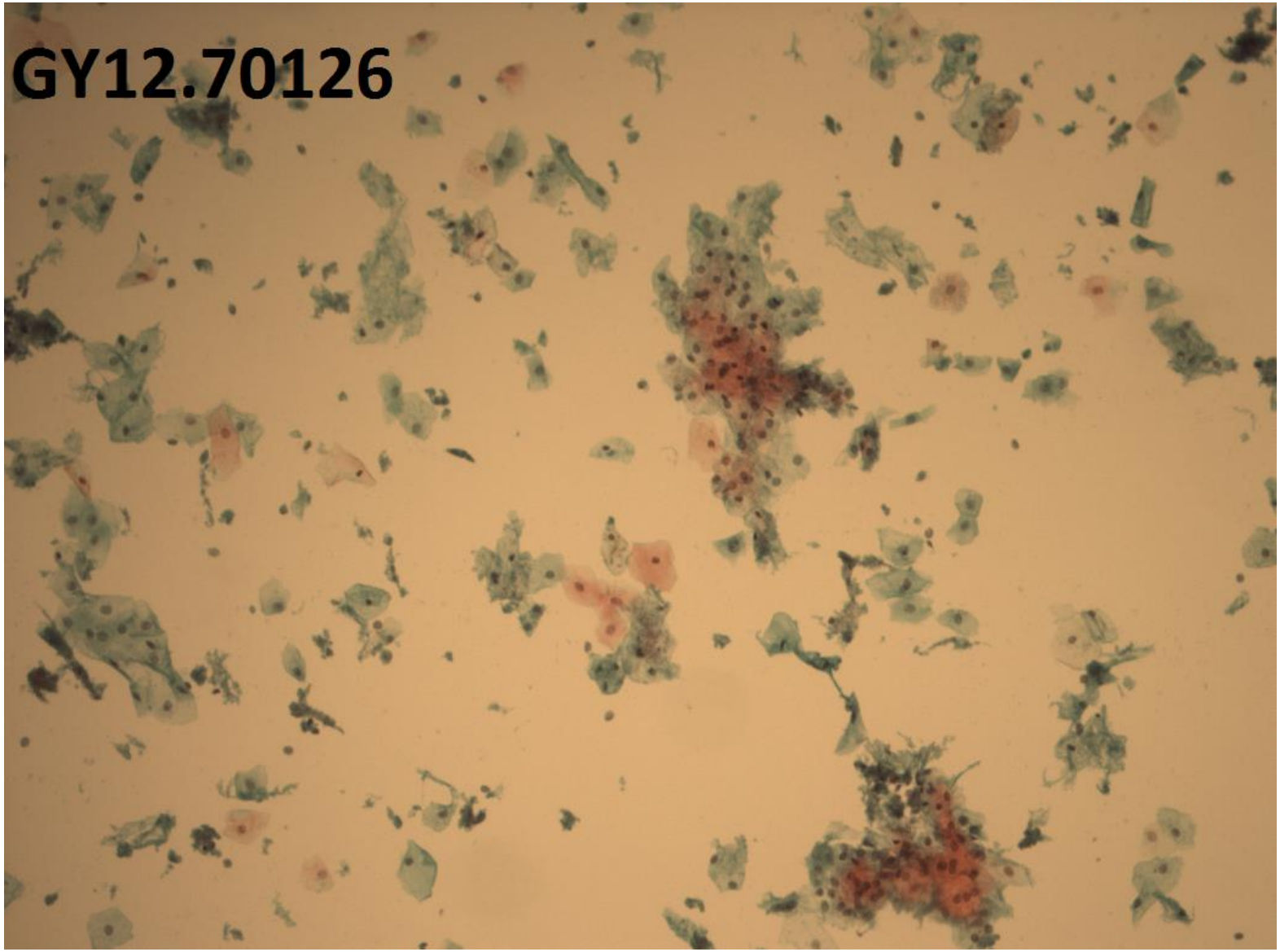

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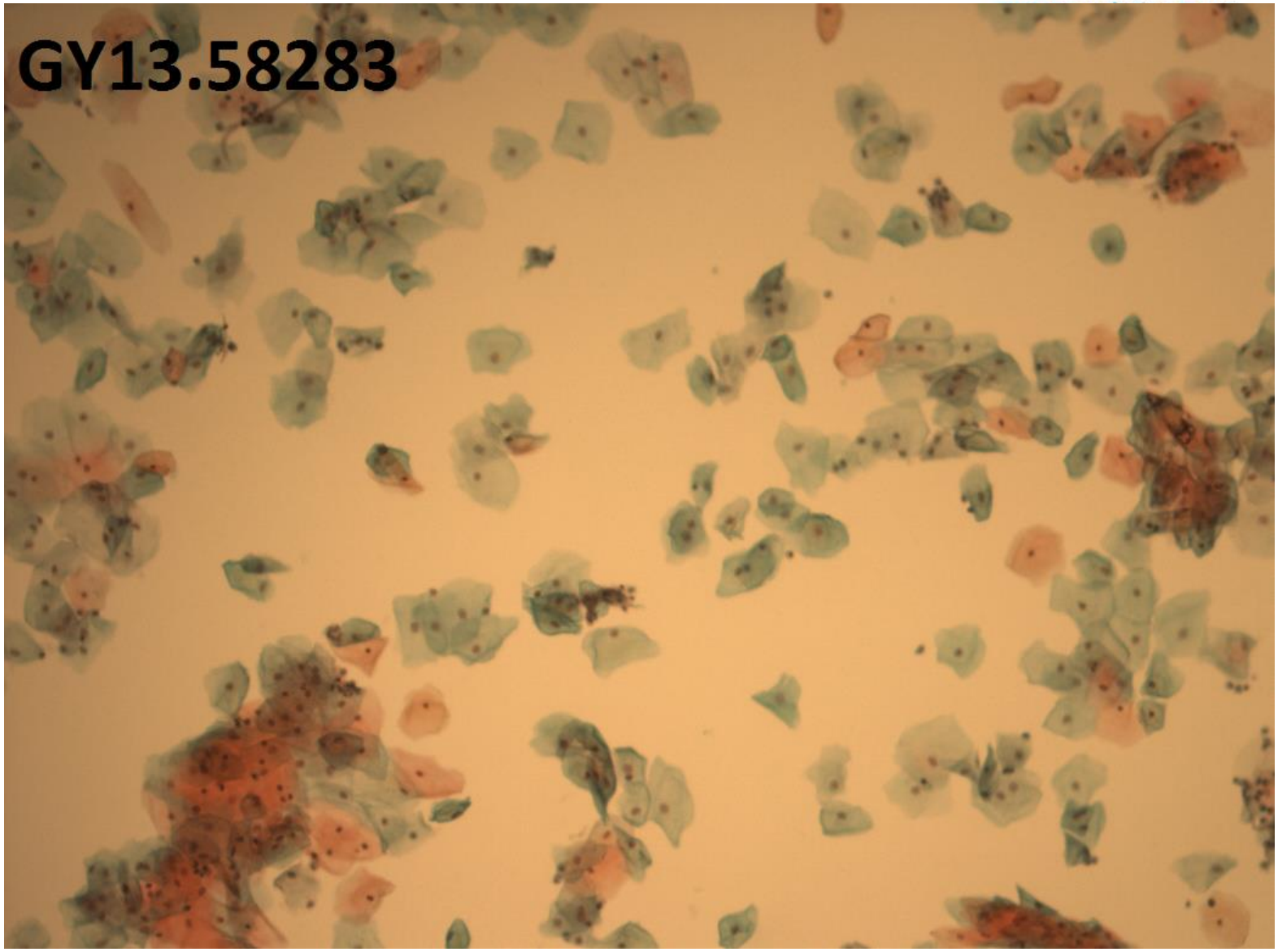

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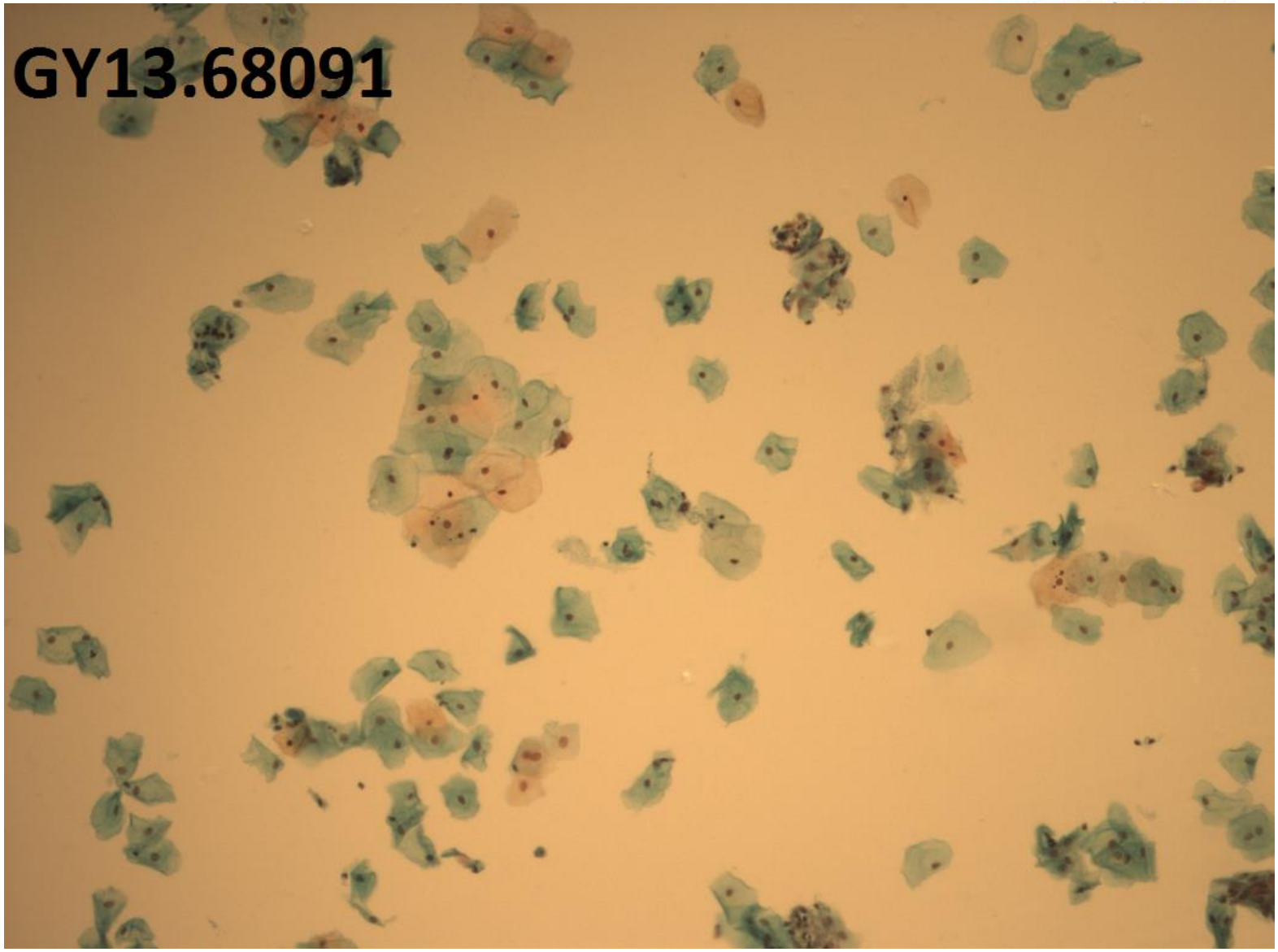

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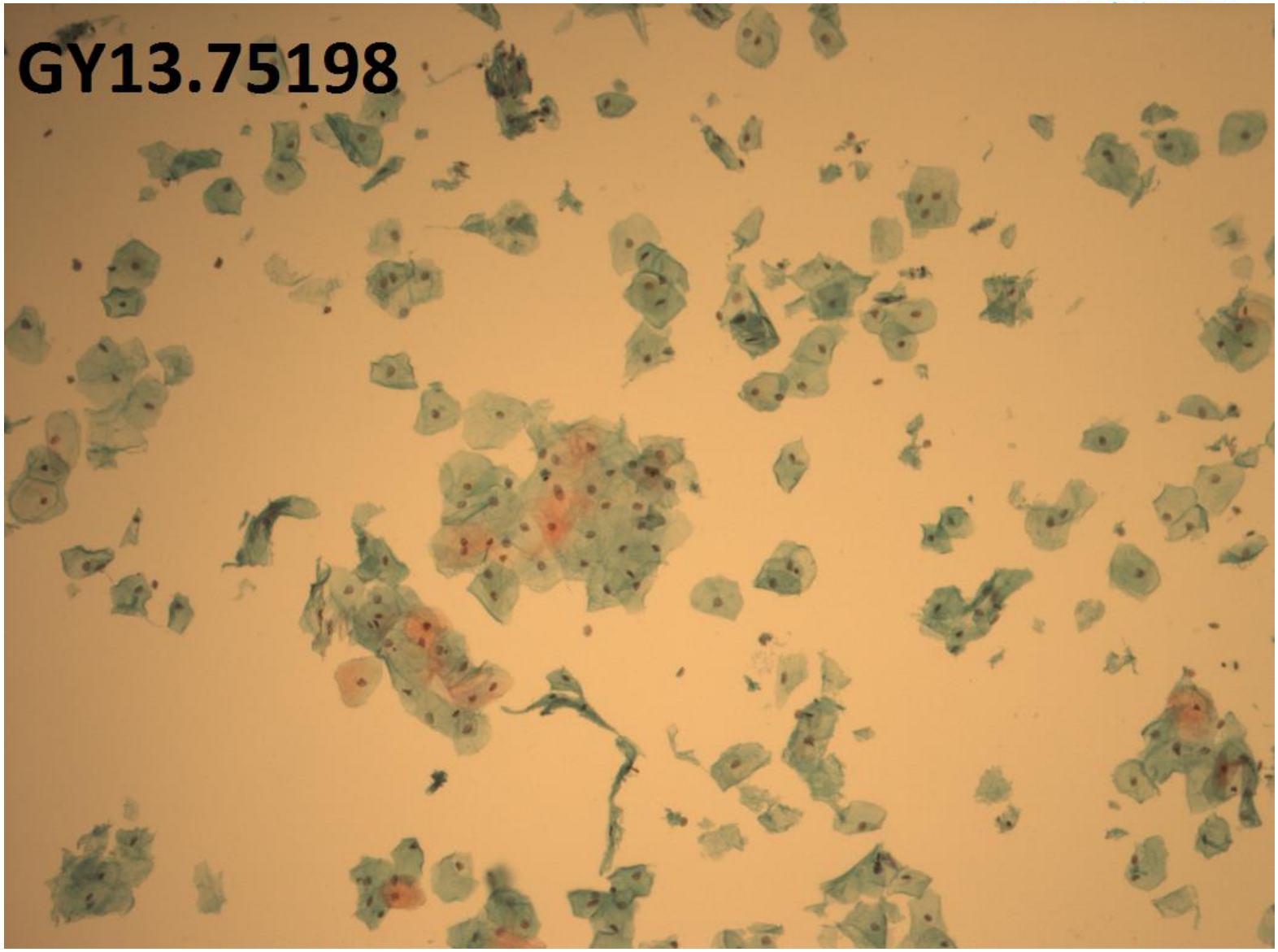

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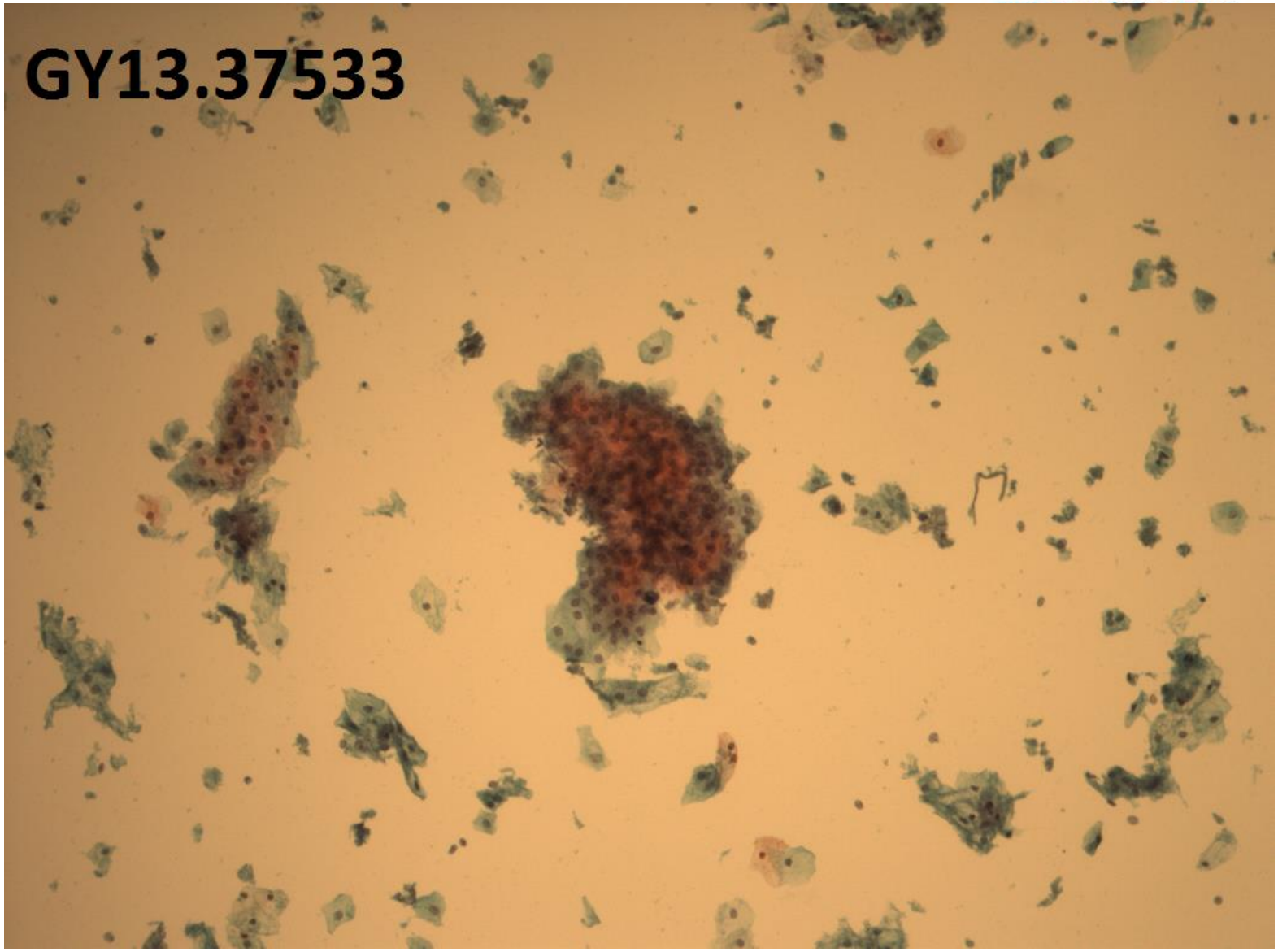

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What do the following cases have in common?

- GY12.70126 – Age 52, Cytology borderline
- GY13.58283 – Age 40, Cytology borderline
- GY13.37533 – Age 28, Cytology negative
- GY13.68091 – Age 40, Cytology borderline
- GY13.75198 – Age 41, Cytology borderline

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What do they have in common?

- All subsequently diagnosed with cervical cancers
- 3 in next screening round, 2 interval
- All tested with HC2
- All tested negative

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HC2 neg cancer details

Interval

- GY13.58283 – Age 40, 2b SCC
- GY12.70126 – Age 52, 1b1 SCC

Next Screening round

- GY13.37533 – Age 28, 1a1 SCC, Next test 4
- GY13.68091 – Age 40, 1b1 SCC, Next test 4
- GY13.75198 – Age 41, 1a1 SCC, Next test 7

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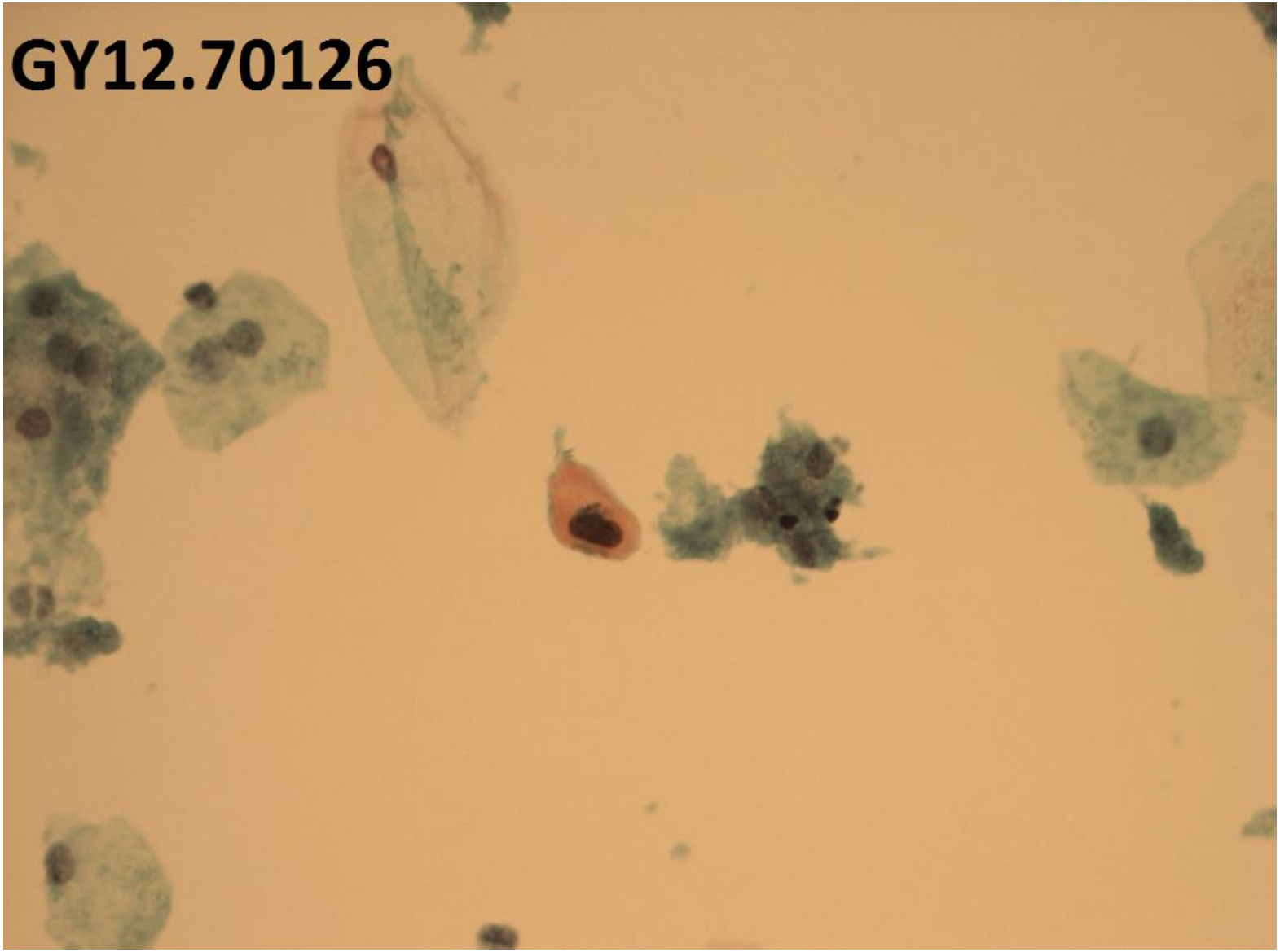
GY12.70126



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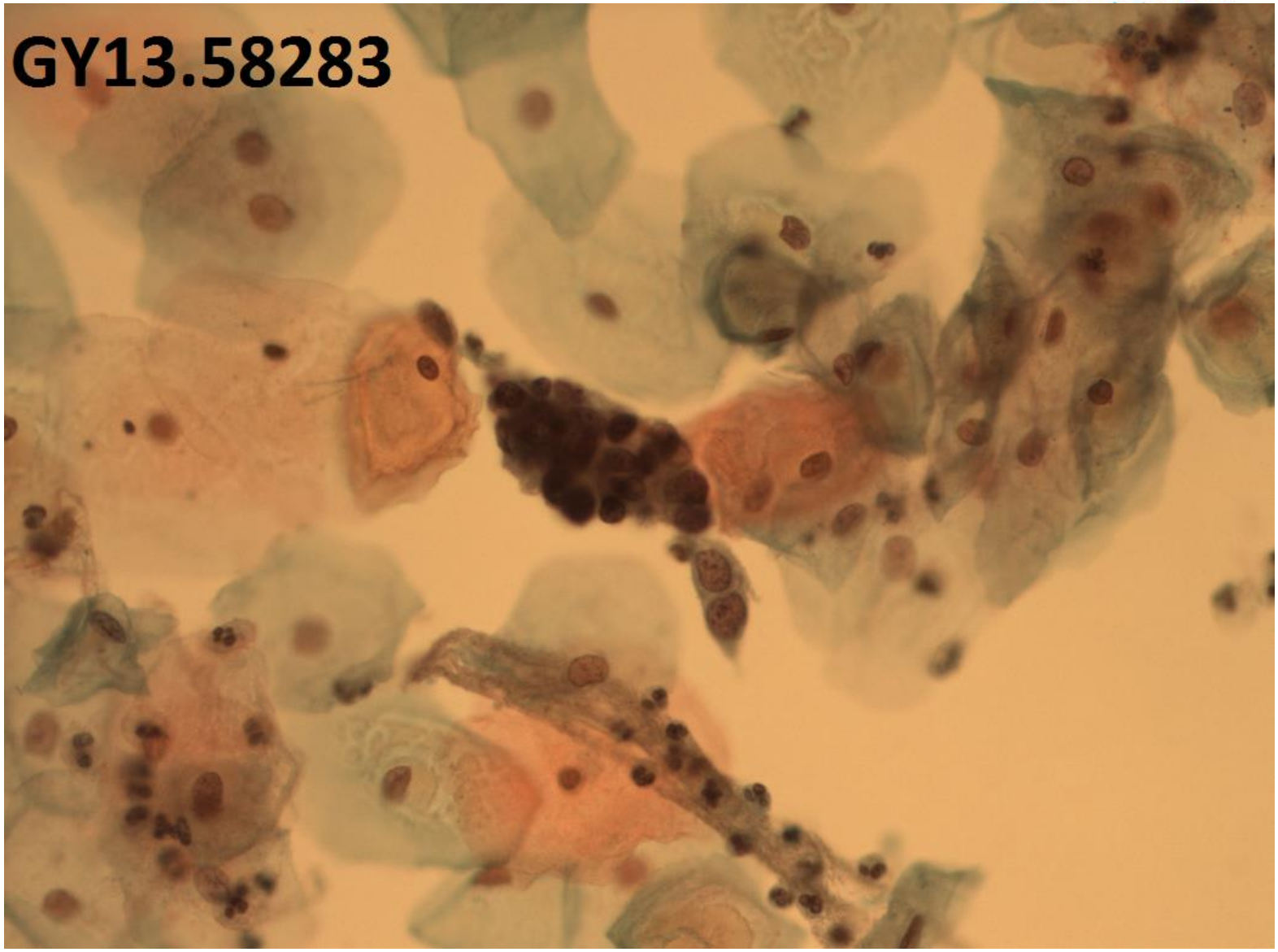

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HC2 neg cancers – test details

	HC2 Result (Cut off = 2 RLU)	No of negs in run	No of negs with higher RLU
GY13.58283	1.11	8	0
GY12.70126	0.97	8	0
GY13.37533	0.66	48	3
GY13.68091	0.37	65	8
GY13.75198	0.28	46	2

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Reports of cervical cancers with negative HR HPV test

- Kaiser Permanente – 37%

Katki HA, Kinney WK, Fetterman B, Lorey T, Poitras NE, Cheung L, et al. Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: a population-based study in routine clinical practice. Lancet Oncol. 2011;12(7):663–672.

- *Multi-centre study – 22.7%*

Zhao C, Nayar R, Levi AW, et al. Prior high-risk HPV testing and Pap test results of 58 invasive cervical carcinomas diagnosed in 2012. JASC. 2013; 2:S3.

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Gloucestershire lab data – HC2 era

- All cervical cancers (Glos and Worcs) N =197
- With HPV test N = 26
- With negative HPV test at or since previous screening cycle N = 5
- 19.2% of cancers tested were negative with HC2 within 3 years of diagnosis

BUT PLEASE REMEMBER

- National (English) rate for false negative cytology on review following a cancer diagnosis is around 15% -20% (Cancer audit data)

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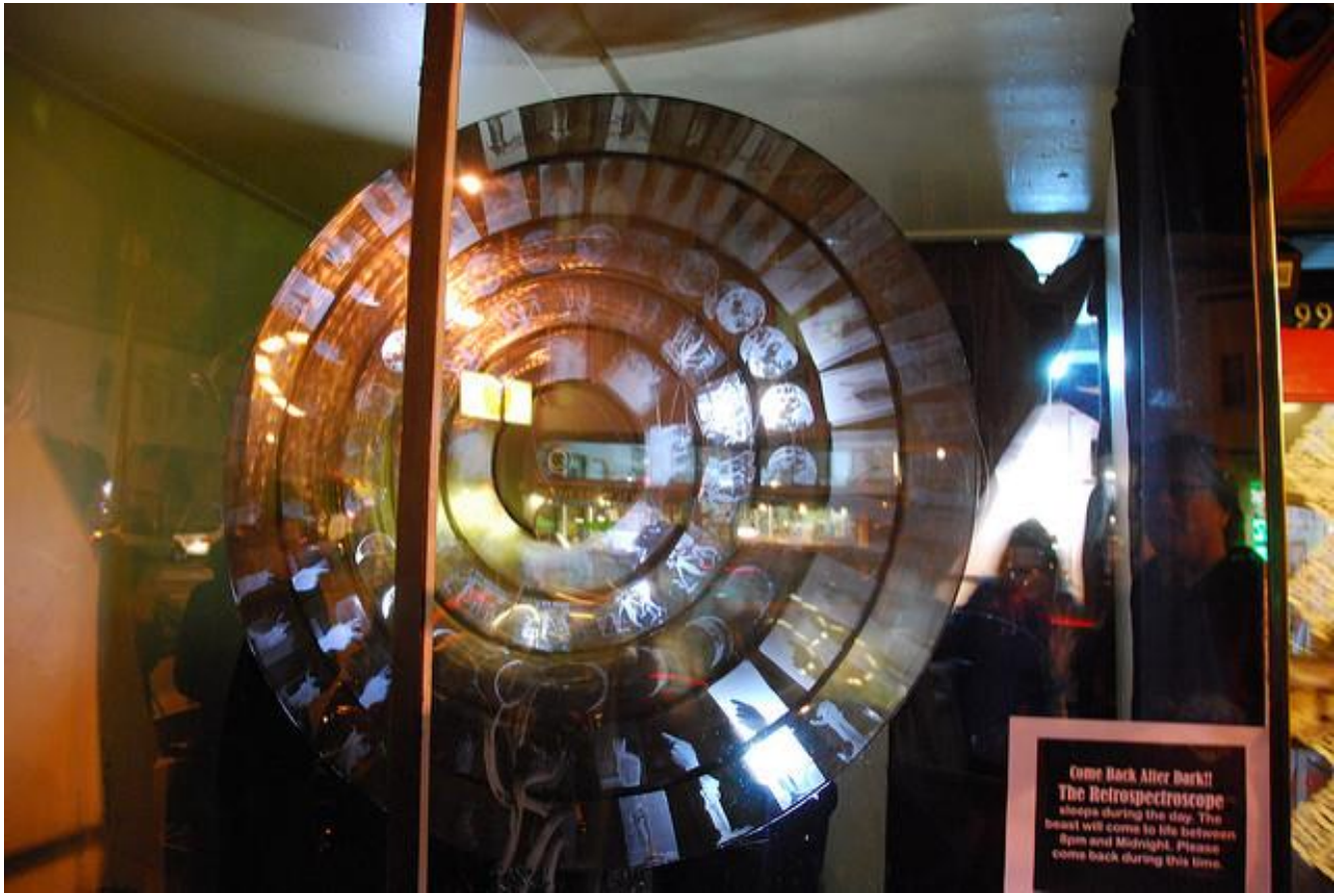
Useful tools in cytology 1 – the retrospectroscope



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'Handful of changes' make cancer

- 19th October 2017
- British scientists have worked out it takes only between one and 10 mutations – depending on the type of tumour – to transform a healthy cell into a cancer. The team, at the Wellcome Trust Sanger Institute, also found half the mutations identified were in genes that had never been implicated in cancer before.
- http://www.bbc.com/news/health-41644020

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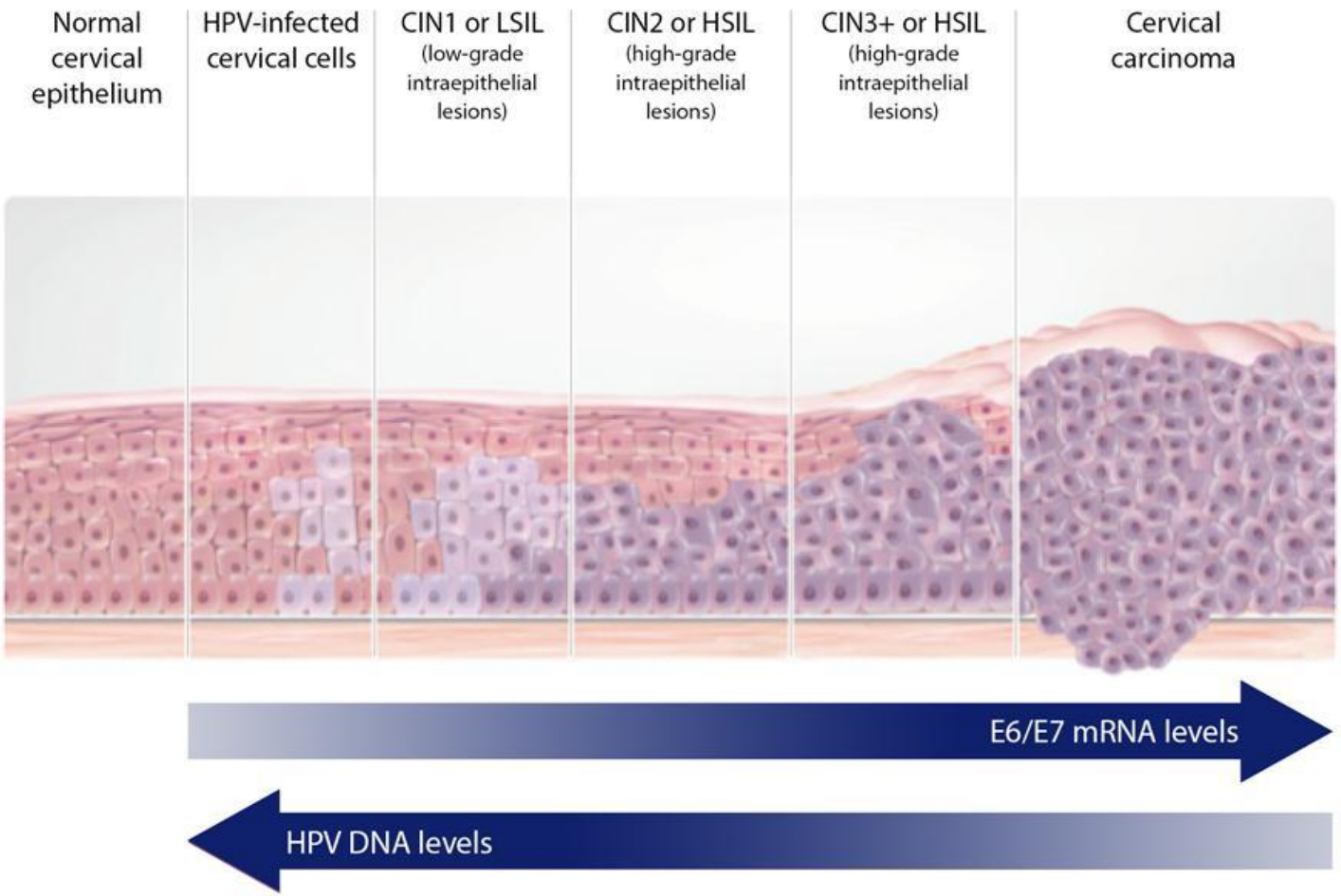
DNA vs RNA



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2015 - Reprocurement

Same 5 systems as 2012 except……

- Genprobe acquired by Hologic
- Future of Cervista unclear
- 2 cancers known to have tested HR HPV neg with HC2
- Local model still preferred to run within cytology
- NHS CSP TOC data
- Subsequently two more systems added – BD Onclarity and Cepheid Expert.

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Useful tools in cytology 2 – the crystal ball

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HR-HPV TOC Data

Public Health England

Significance of these results

	Difference	95% CI
SP, Roche Sheffield	1.5	1.14-1.7
SP, Roche Liverpool	3.5	1.95-6.29
SP, Roche S+L	1.9	1.48-2.44
SP, Abbott, Manchester	1.12	0.98-1.27
SP, Genprobe, Liverpool	1.34	1.04-1.73
TP, Roche, Norwich	1.24	1.04-1.44
TP, Genprobe, Kettering	0.84	0.69-1.03
TP, Abbott, NP	1.04	0.84-1.29
TP, Cervista, Taunton	1.41	1.15-1.74

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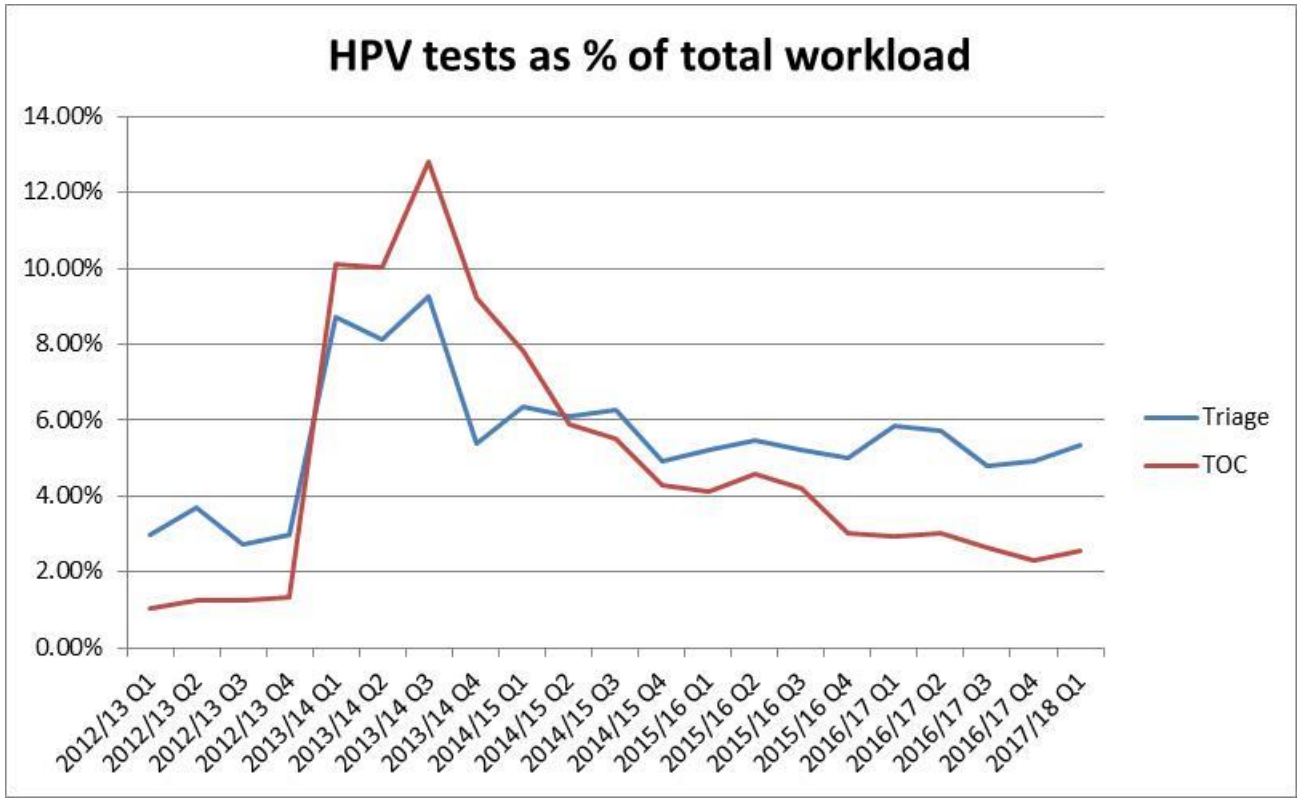
The first 6 years - Aptima HR HPV test volumes



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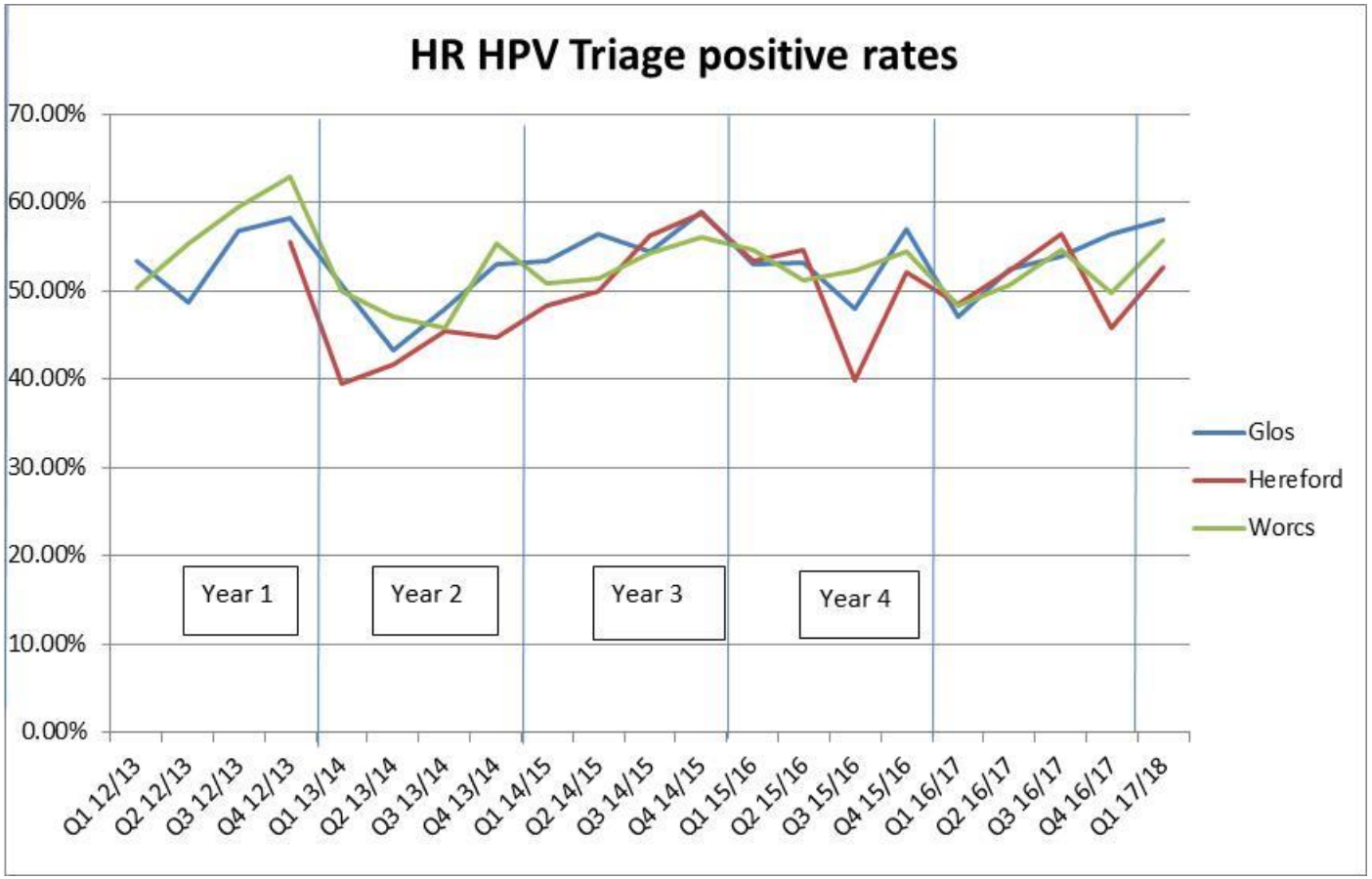
The first 6 years - Aptima HR HPV test results



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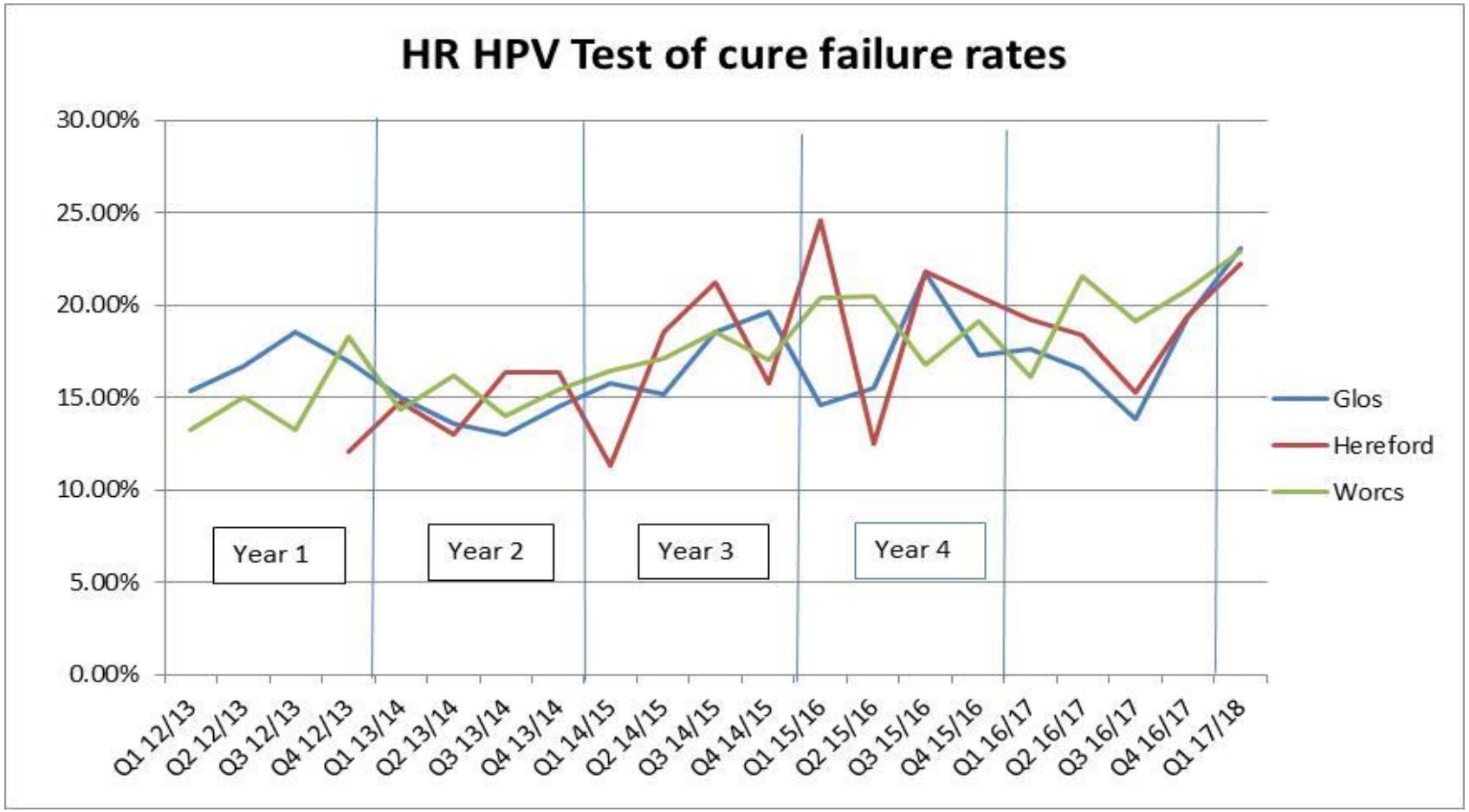
The first 6 years - Aptima HR HPV test results



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Colposcopy referral patterns

	HPV test	Inad	Low grade no HPV	Neg HPV +ve	Low grade HPV +ve	High grade	Total
2011-12	None	0.07%	1.50%	0.00%	0.00%	1.06%	2.63%
2012-13	HC	0.06%	0.93%	0.00%	1.84%	1.02%	3.85%
2013-14	HC	0.06%	0.00%	0.10%	4.48%	1.13%	5.77%
2014-15	HC	0.06%	0.00%	2.12%	3.61%	1.19%	6.98%
2015-16	AP	0.03%	0.00%	1.12%	3.01%	1.06%	5.22%
2016-17	AP	0.02%	0.00%	0.47%	2.61%	1.14%	4.23%

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Gloucestershire cytology reporting risk profile - risk of CIN2+			
	2011/12	2013/14	2015/16
	No HPV	HC2	AP
Borderline	12.45%	24.22%	32.15%
Mild	22.88%	20.56%	23.26%
Moderate	82.39%	77.66%	80.26%
Severe	95.73%	94.56%	92.35%

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Cervical Cytology Reporting Risk profile – 2 Borderline changes in Endocervical cells

- NHSCSP Document 20 (March 2016)

The limited available UK data indicate that a borderline classification of abnormal glandular cells is associated with a low, but significant, increase in the incidence of pathology, with high-grade CIN being detected in 10% to 33% of cases, and invasive disease in 1.8% to 22% of cases. Intraepithelial glandular lesions are detected in less than 10% of cases.[68,193,205,206] The above guideline conforms with the suggestions of a joint college working party which did not suggest a need for radical excision of the endocervix.[207] One study showed that when directed biopsy was compared with loop or cone biopsy, no significant advantage in diagnostic accuracy was obtained with larger biopsies.

- Rate of CGIN or Adenocarcinoma in HR HPV +ve samples in Gloucestershire - > 70%, but very small numbers.

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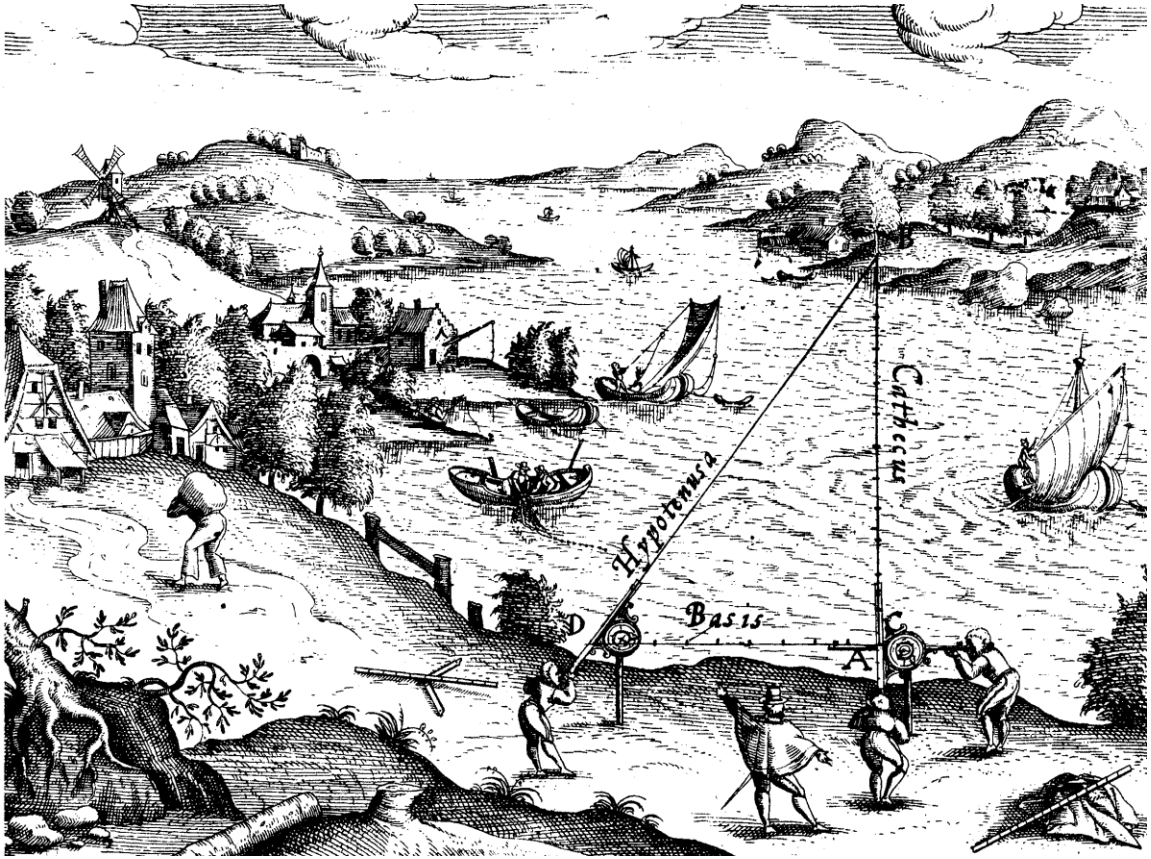
Triangulation

involves using multiple data sources in an investigation to produce understanding.



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Triangulation – a caveat

- Currently no two screening rounds have been the same.
- Confounders to triangulation are:
  - Changing HPV testing protocols
  - Arrival of catch up vaccinated population
  - Coverage
  - Removal of high risk sample taking locations from some programmes
  - Laboratory technology changes

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Triangulation of hypothesis

Implementation of HR HPV Triage and TOC has detected more disease at an earlier stage

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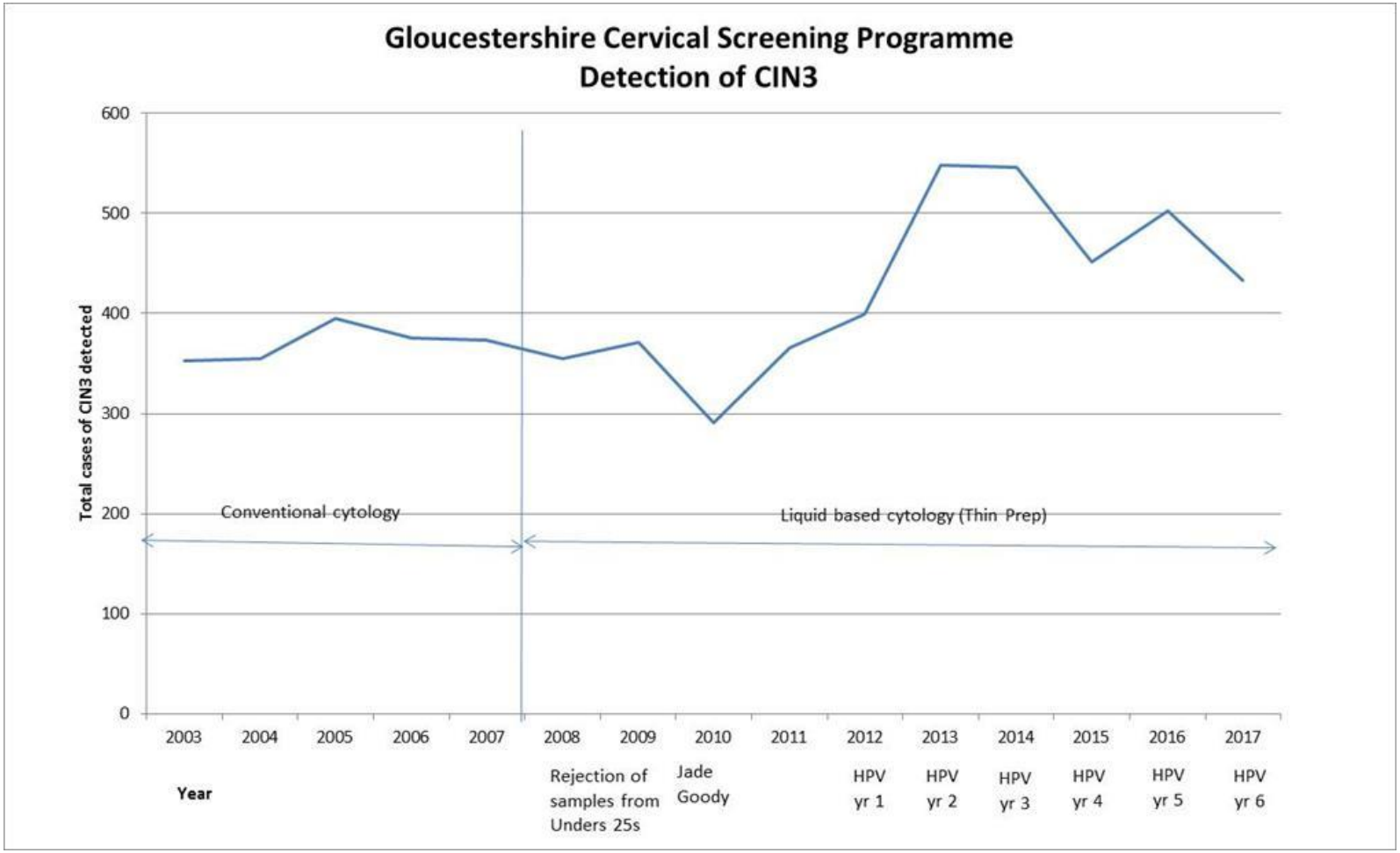
CIN3 in Gloucestershire



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CIN3 – pathway to detection in 2016

Routine screening – 79.40%

- Routine recall, last test neg no HR HPV – 41.69%
- First test – 32.75%
- Routine recall, last test HR HPV +ve, colp neg 4.96%

Untreated low grade disease

- CIN1 pathway – 7.44%
- LG Cytology only – 2.23%

Following treatment

- For CIN – 2.73%
- For cancer – 0.50%

Unknown – 7.69%

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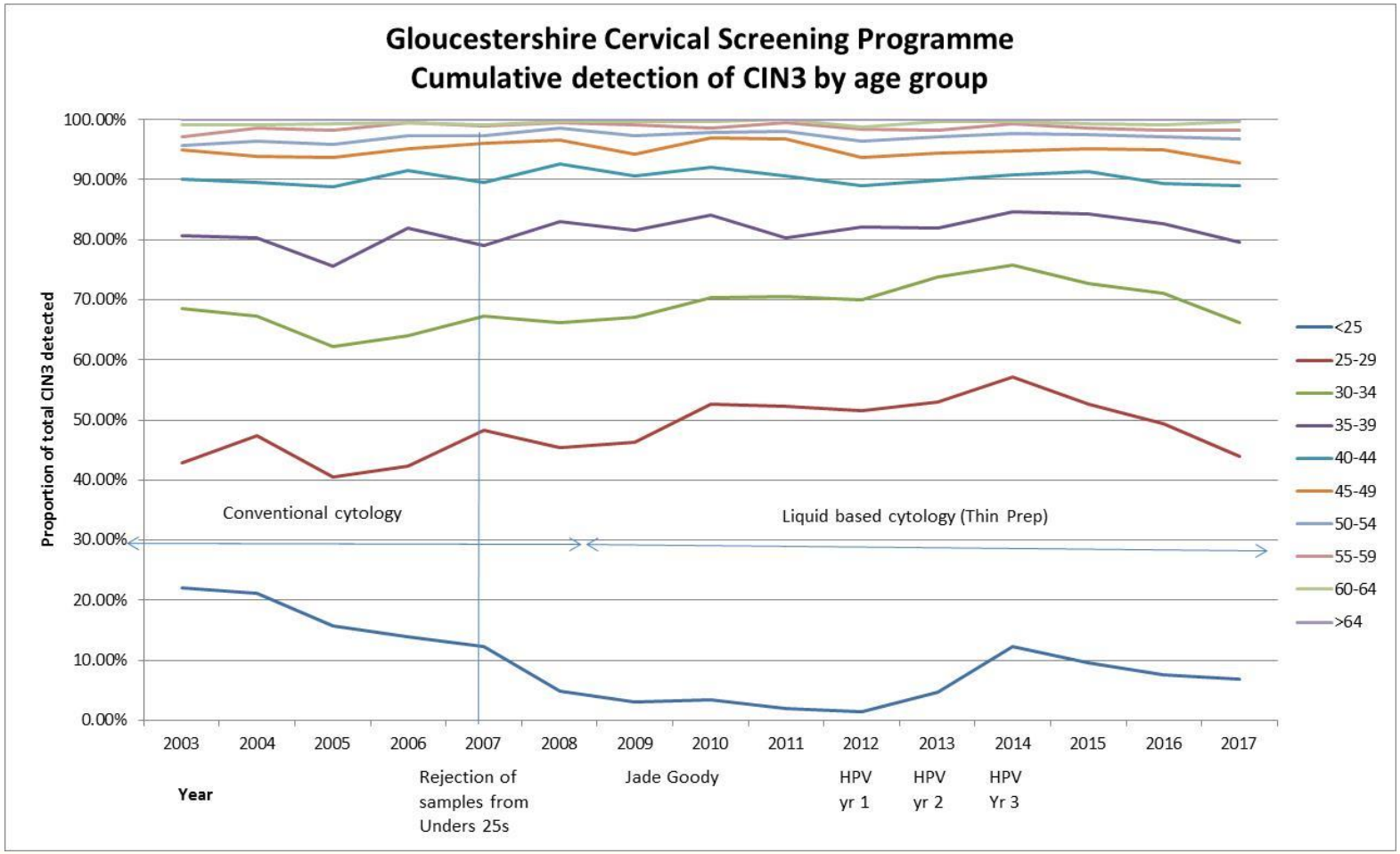
CIN3 in Gloucestershire
Catch up vaccinated cohort



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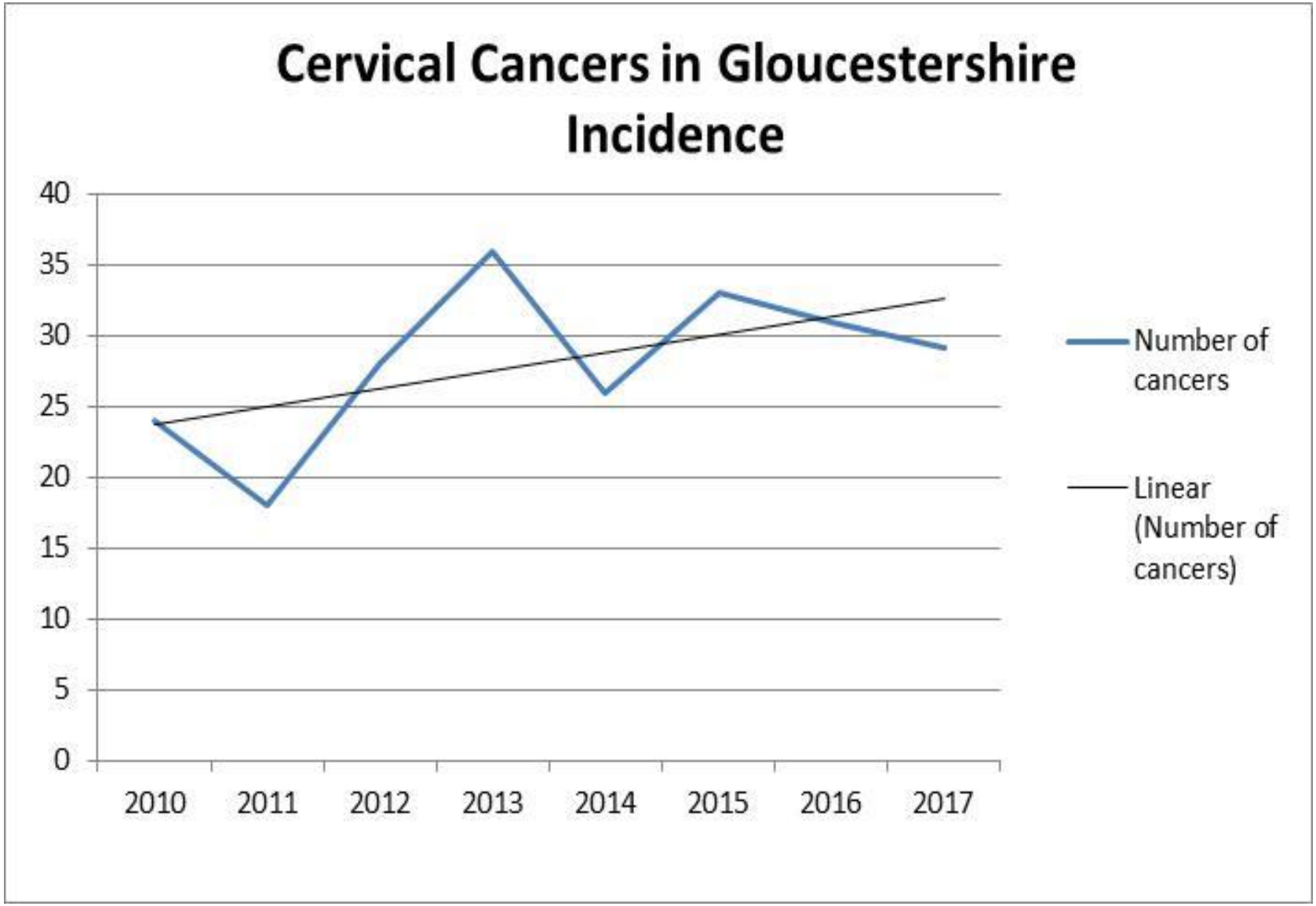

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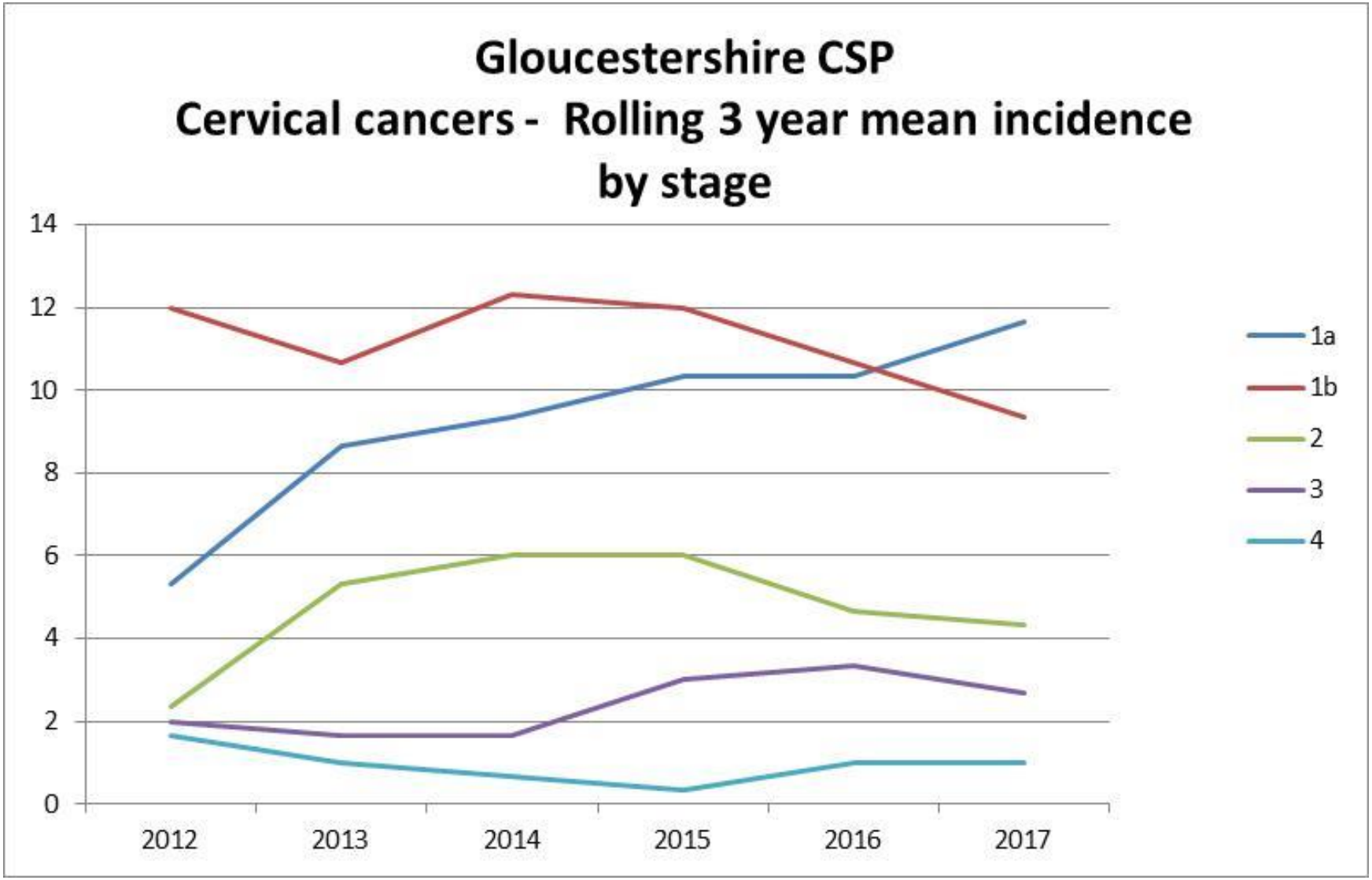

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Triangulation of hypothesis
Implementation of HR HPV Triage and TOC has detected more disease at an earlier stage

Primary data – amount of CIN3 detected

Triangulation -

- Number of 1a cancers has increased whilst number of 1b cancers has decreased
- Reporting risk profile suggests more HG disease coming from borderline cytology HR HPV +ve – but not from mild dyskarosis
- Cytology HG pick up rate stable

Several biological gradients correlate with hypothesis

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Thanks

- All cytology staff in Gloucestershire laboratories
- Richard Butt
- Sarah O'Flaherty
- Karol Baxter
- Nichole Villeneuve
- Steve Ferryman
- Jo Underhill (Worcestershire)
- Adrian Smith (Hologic)
- Alex Castanon (CRUK)

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