

Is a single HPV DNA test effective in triaging women with low-grade abnormal cytology to cytological surveillance or colposcopy?  
Results from the UK TOMBOLA trial

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# Background

UK:

- Organised smear-based cervical screening programmes
- 3/5 yearly screening between ages 20/25 and 60/64 years; in primary care
- 250,000 smears each year showing low-grade abnormalities (BNA or mild dyskaryosis)
- How should these women be managed?

# Management of women with low-grade smears

- How should these women be managed?  
Cytological surveillance OR referral for colposcopy examination?  
Effectiveness in detecting CIN2 or more severe disease (CIN2+), now and into the future ?
- Should we triage women on the basis of high-risk HPV DNA status? (i.e. is there a role for HPV testing in determining management?)
  - refer HPV+ve women for colposcopy?
  - manage HPV–ve women by surveillance?

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- Should we triage women on the basis of high-risk HPV DNA status? (i.e. is there a role for HPV testing in determining management?)
  - refer HPV+ve women for colposcopy?
  - manage HPV–ve women by surveillance?
- In HPV+ve women, is colposcopy more effective in detecting CIN2+ than cytological surveillance?
- In HPV-ve women, are cytological surveillance and colposcopy equally effective in detecting CIN2+?
- Test for interactions between management and HPV status in an RCT where women are followed for 3 years

**Recruitment of eligible women**  
*(resident Tayside, Grampian, Nottingham, age 20-59, recent low-grade smear +/- previous BNA, no previous treatment for CIN)*

**Randomisation R1** N=4439 women;  
52% of eligible

Repeat smears

Initial colposcopy

**Randomisation R2** N=1983 women

Immediate LLETZ

Punch biopsy & recall for LLETZ

**Exit examination - colposcopy and treatment if required**

3 years

# HPV testing

- Cervical swab taken at trial recruitment.
- Consensus GP5+/6+ primers and 14-probe cocktail to detect high-risk types - 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.
- HPV results not revealed. Management not based on HPV result.
  - therefore, we evaluated - without bias – the effectiveness of colposcopy vs surveillance in HPV+ve women and in HPV-ve women.

# HPV status at recruitment & CIN2+: 3-year follow-up

	CIN2+	No CIN2+	Total
hrHPV positive			1755
hrHPV negative			2056
Total	752	3279	4031

44%  
HPV+ve

19% CIN2+ by 3 years  
(10% CIN3+)


# HPV status at recruitment & CIN2+: 3-year follow-up

	<b>CIN2+</b>	<b>No CIN2+</b>	<b>Total</b>
<b>hrHPV positive</b>	532	1223	1755
<b>hrHPV negative</b>	220	2056	2056
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hrHPV positive	532	1223	1755
hrHPV negative	220	2056	2056
Total	752	3279	4031

30% of women who had CIN2+ detected were hrHPV-ve

70% of those who were hrHPV+ve did not have CIN2+

# Comparing management policies in HPV+ve and HPV-ve women: CIN2+

HPV status	Management	% with CIN2+	Cumulative Incidence	RR (95% CI)
+ve		30%	114 / 1000	
-ve		10%	36 / 1000	

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	surveillance		30	1 (reference)
	colposcopy		41	1.4 (1.0-1.8)

# Comparing management policies in HPV+ve and HPV-ve women: CIN2+

HPV status	Management	% with CIN2+	Cumulative Incidence	RR (95% CI)	
+ve		30%	114 / 1000		
	surveillance		95	2.3 (1.8-3.0)	1.0 (reference)
	colposcopy		134	3.3 (2.6-4.2)	1.4 (1.2-1.7)
-ve		10%	36 / 1000		
	surveillance		30	1 (reference)	
	colposcopy		41	1.4 (1.0-1.8)	

p(interaction)=0.76

# Comparing management policies in HPV+ve and HPV-ve women: CIN3+

HPV status	Management	% with CIN3+	Cumulative Incidence	RR (95% CI)	
+ve		17%	65 / 1000		
	surveillance		57	3.0 (2.1-4.3)	1.0 (reference)
	colposcopy		73	3.9 (2.7-5.5)	1.3 (1.0-1.6)
-ve		4%	15 / 1000		
	surveillance		13	1 (reference)	
	colposcopy		16	1.2 (0.8-1.8)	

p(interaction)=0.87

# Summary

- 30% of those with CIN2+ by 3 years were hrHPV-ve.
- 70% of those hrHPV+ve did not have CIN2+ by 3 years.
- In HPV+ve women, little benefit of colposcopy over cytological surveillance - especially for CIN3+.
- In HPV-ve women, cytological surveillance and colposcopy are equally effective – especially for CIN3+.

# Conclusions

- Single HPV test not useful in determining which women should be referred to colposcopy.
- Cytological surveillance (6 monthly smears in primary care) is sufficient for women with low-grade smears, regardless of HPV status.



# Conclusions

- Single HPV test not useful in determining which women should be referred to colposcopy.
- Cytological surveillance (6 monthly smears in primary care) is sufficient for women with low-grade smears, regardless of HPV status.
- Findings of this large, population-based, RCT are contrary to current trends in management in UK (increased colposcopy referrals, HPV pilot). How best to transfer knowledge into practice?

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## TOMBOLA Group

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**Hull** - Leslie Walker



# Properties of a single HPV test: cross-sectional analysis in colposcopy arm

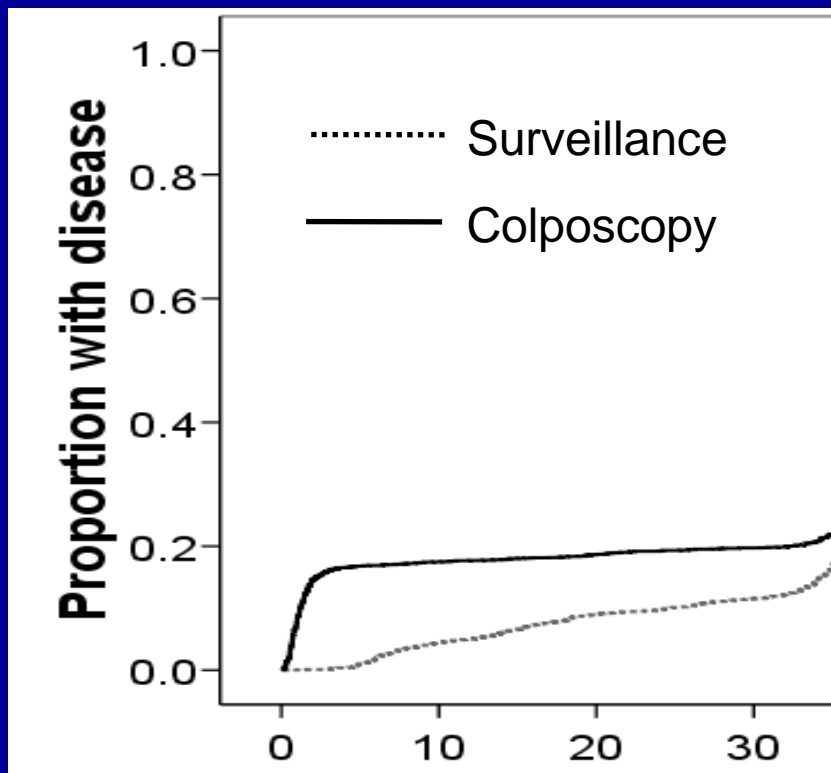
	smear status	Mild	BNA
	age	20-59	20-59
% with CIN2+		31%	12%
% hrHPV positive		60%	34%
Sensitivity of HPV test <i>(probability that woman with CIN2+ will be identified by positive HPV test)</i>		75%	70%
Specificity of HPV test <i>(probability that woman with no CIN2+ will be identified by negative HPV test)</i>		47%	71%
PPV of HPV test <i>(probability that woman with positive HPV test has CIN2+)</i>		39%	25%
NPV of HPV test <i>(probability that woman with negative HPV test has no CIN2+)</i>		81%	95%

# Properties of a single HPV test: cross-sectional analysis in colposcopy arm

	smear status age	Mild		BNA	
		20-59	40-59	20-59	40-59
% with CIN2+		31%	13%	12%	4%
% hrHPV positive		60%	40%	34%	14%
Sensitivity of HPV test <i>(probability that woman with CIN2+ will be identified by positive HPV test)</i>		75%	65%	70%	31%
Specificity of HPV test <i>(probability that woman with no CIN2+ will be identified by negative HPV test)</i>		47%	64%	71%	87%
PPV of HPV test <i>(probability that woman with positive HPV test has CIN2+)</i>		39%	22%	25%	9%
NPV of HPV test <i>(probability that woman with negative HPV test has no CIN2+)</i>		81%	92%	95%	97%

# Main findings: 3 year follow-up

Management	% with CIN2+	Cumulative Incidence	RR (95% CI)
Surveillance	16%	58 / 1000	1 (reference)
Colposcopy	21%	79 / 1000	1.37 (1.19-1.57)



- Most of difference due to CIN2
- RR CIN3+ = 1.26 (1.04-1.53)
- Large number of colposcopy referrals where no CIN2+ is found.

# Biopsy vs immediate LLETZ: CIN2+

HPV test	Management	Cumulative Incidence	RR (95% CI)
+ve		139 / 1000	
+ve	Biopsy	132	2.07 (1.53-2.79)
+ve	Imm LLETZ	146	2.24 (1.66-3.01)
-ve		42 / 1000	
-ve	Biopsy	46	1 (reference)
-ve	Imm LLETZ	39	0.85 (0.60-1.22)

p(interaction)=0.27

# Biopsy vs immediate LLETZ: CIN3+

HPV test	Management	Cumulative Incidence	RR (95% CI)
+ve		74 / 1000	
+ve	Biopsy	72	3.23 (1.99-5.24)
+ve	Imm LLETZ	76	3.25 (2.01-5.26)
-ve		16 / 1000	
-ve	Biopsy	15	1 (reference)
-ve	Imm LLETZ	18	1.17 (0.60-2.07)

p(interaction)=0.66