



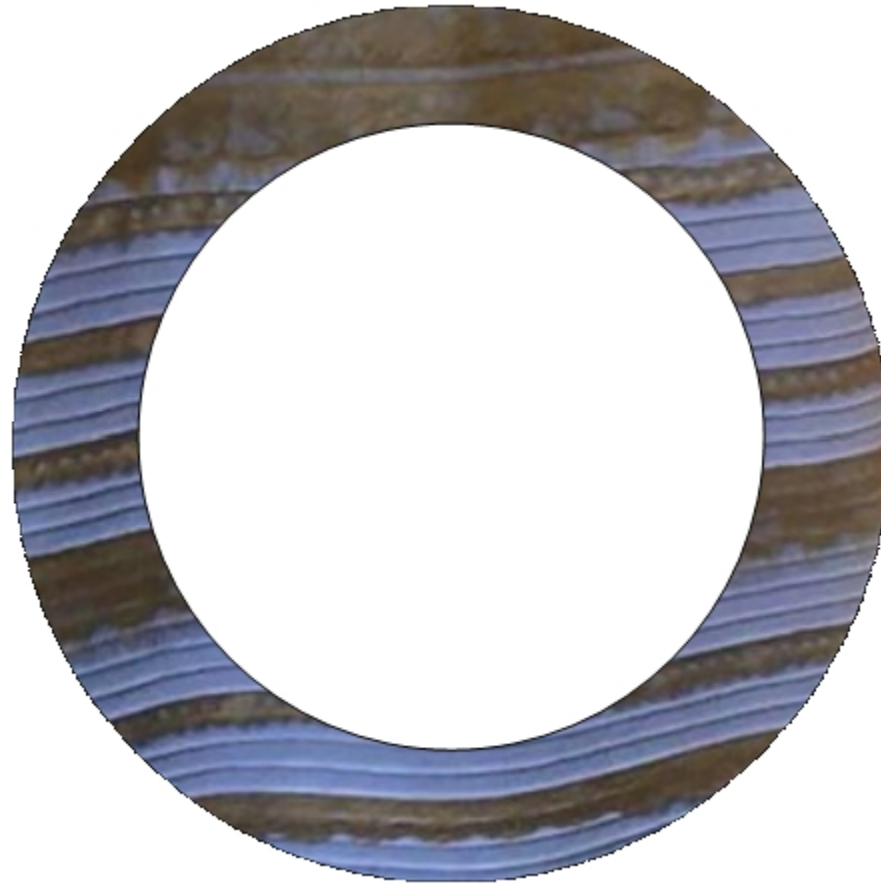
Pregnancy Testing Concerns

The Ides of March: Et Tu, Quidel?

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Any Unusually Colored Rings lately?



For women with regular 28 day cycles (Thanks to Jeanna Piper for slide)

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
1 Menses	2	3	4	5	6	7
8	9	10	11	12	13	14
15 Ovulation / fertilization	16	17	18	19	20	21
22	23	24	25	26 Serum hCG Mostly + (25 mIU/mL) Urine -	27 Urine +/-, most negative	28 Urine +/- mixed
	Implantation					
		Serum hCG +/- mostly negative	Serum hCG +/- mixed			
29 Expected next menses/missed Urine +/- mostly +	30 Urine + unless delayed ovulation/ implantation	1 Recommend start using home urine hCG testing	2	3	4	5
6	7	8	9	10	11	12

Notes

- hCG detection
 - hCG levels <5 mIU/ml are considered negative
 - >25 are considered positive,
 - 5-25 are considered equivocal
- Serum hCG levels double every ~ 31 hours after implantation
- Serum hCG becomes detectable 3-4 days before day of missed menses (days 10-11 after ovulation).
- Urine hCG levels in first morning urine are half of the serum level, and are even lower in random urine samples.
- Urine hCG levels on day of missed menses in 1 study were 12, 32, 38, 116, and 356 mIU/ml.
- For women not on hormones, cycle lengths longer than 28 days would result in longer times to conception/implantation/detection.
- Timing of ovulation after exposure to exogenous hormones is unpredictable

Quidel Concerns

- In 2011, the SMILE group noted EQA failures with the Quidel kit
- Data was incomplete and lacked rates of kit use
- Most non-USA DAIDS sites switched to Accutest / UKNEQUAS who provides a low positive sample with each kit and informs clients of sample concentrations
- Urine pregnancy rapid tests are CLIA waived and do not require EQA in the USA

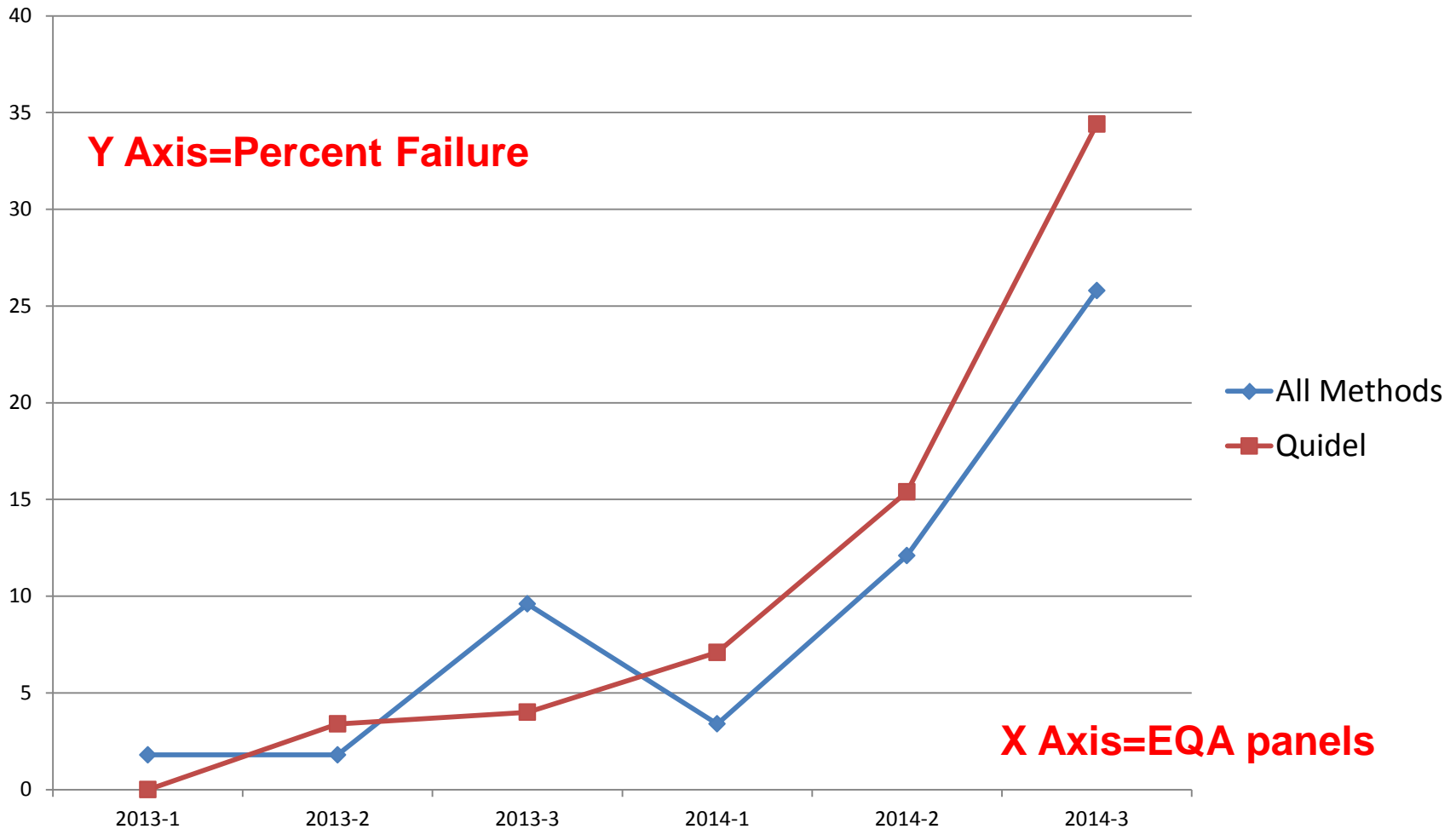
Quidel Concerns-cont.

- In 2014, SMILE raised concerns again and suggested networks switch away from Quidel.
- This led to some networks making operational changes and recommendations to sites, many of which are shared MTN sites.

Quidel EQA Data

- In 2014, 50% of EQA failures at DAIDS labs were from the Quidel kit; 51% of the EQA results came from the Quidel Kit.
- 2013-2014 EQA panels at ASPIRE sites
 - 107 total panels
 - 103 panels had 100%
 - 4 panels failed 1 sample (low concentration sample ~56mIU/mL)
 - 1 of those EQA panels was stuck in customs for 20 days

Percent Pregnancy EQA Failures Over Time: 56 mIU/mL Sample at DAIDS labs



56 mIU/mL sample: Additional Information

- Multiple EQA providers source the 56 mIU/mL sample from the same laboratory, including Accutest and API.
- One pool of the sample was created and has been in use for multiple years.
- The chemistry instrument used to determine the concentration of hCG in the sample does not support a urine hCG test method.
- This is not a pure human urine sample.

SAS Low Positive Control Set

- SAS Control set contains 250 mIU/mL and 25 mIU/mL samples. Not made specifically for Quidel.
- MTN LC sourced and sent to several ASPIRE sites.
- All controls working thus far-results still incoming.

Quidel Performance in the Field

	VOICE	ASPIRE	ACTG	Total
Enrolled	5027	2629	4731	12378
Positive Quidel Month 1	21	8	5*	34
Rate	0.42%	0.3%	0.1%	0.27%

* Within 4 weeks of enrollment

Quidel Performance in the Field

- Jeanna Piper did additional analysis on the 29 MTN pregnancies at Month 1
- This analysis was based on criteria such as date of last menstrual period and Ultrasound results
- VOICE:
 - 2/21 should have been detected by a urine pregnancy test if their dates were correct, *but their dates could not be confirmed*
 - 4/21 would have been caught by serum testing (includes 2 above)

Quidel Performance in the Field

- ASPIRE:
 - 0/8 could have been detected by urine pregnancy testing at the time of enrollment
 - 1/8 would have been detected by serum testing
- **Overall, 2/5027 women in VOICE and 0/2629 women in ASPIRE had pregnancies potentially missed by urine testing at enrollment for a total of 2/7256 (0.027%)**

MTN Strategy

- Focus on sites who fail EQA sample
- Focus on likely factors: EQA material, operator error, Clerical errors, kit handling
- Stress importance of proper execution of test, procedures to minimize clerical errors
- Good relations with participants to minimize “Urine Swapping”

Conclusion

No changes to ASPIRE pregnancy testing unless new compelling evidence or data becomes available.