Pregnancy Testing Concerns
The Ides of March: Et Tu, Quidel?

Edward Livant BS, MPH
MTN Laboratory Center
Any Unusually Colored Rings lately?
<table>
<thead>
<tr>
<th>Sunday</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
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<tbody>
<tr>
<td>Menses</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
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<td>10</td>
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<td>12</td>
<td>13</td>
<td>14</td>
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<tr>
<td>Ovulation / fertilization</td>
<td>16</td>
<td>17</td>
<td>18</td>
<td>19</td>
<td>20</td>
<td>21</td>
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<tr>
<td>22</td>
<td>23</td>
<td>24</td>
<td>Implantation</td>
<td>25</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>Serum hCG +/- mostly negative</td>
<td>Serum hCG +/- mixed</td>
<td>26 Serum hCG Mostly + (25 mIU/mL)</td>
<td>Urine -</td>
<td>27 Urine +/-, most negative</td>
<td>28 Urine +/- mixed</td>
<td></td>
</tr>
<tr>
<td>Expected next menses/missed Urine +/- mostly +</td>
<td>29</td>
<td>30</td>
<td>1 Recommend start using home urine hCG testing</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>29</td>
<td>30</td>
<td>1</td>
<td>Recommend start using home urine hCG testing</td>
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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
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

Y Axis=Percent Failure

X Axis=EQA panels

- All Methods
- Quidel
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

<table>
<thead>
<tr>
<th></th>
<th>VOICE</th>
<th>ASPIRE</th>
<th>ACTG</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled</td>
<td>5027</td>
<td>2629</td>
<td>4731</td>
<td>12378</td>
</tr>
<tr>
<td>Positive Quidel Month 1</td>
<td>21</td>
<td>8</td>
<td>5*</td>
<td>34</td>
</tr>
<tr>
<td>Rate</td>
<td>0.42%</td>
<td>0.3%</td>
<td>0.1%</td>
<td>0.27%</td>
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</table>

* 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.