98%, 99%, 100%, and 0%, for SSA, SSB, RNP, Sm, and Scl-70, respectively. The three patients with CIE revealed symptoms typical for systemic lupus erythematosus, SS, mixed connective tissue disease, and SSc, respectively. The three patients with CIE results for Scl-70 had symptoms typical for scleroderma. These data confirm the previously reported (1) excellent sensitivities and specificities of DB techniques for the detection of antibodies against ENAs. The agreement between CIE/IF and DB for the detection of the cytoplasmatic antigens Jo-1 and M2 was 100% and 81–0.99, respectively. The patients with IF+ for M2 had autoimmune hepatitis and chronic hepatitis C.

IF detects various subtypes of antimitochondrial antibodies, but lacks the ability to detect specific antigens, such as the M2 subtype, which is highly specific for primary biliary cirrhosis. Therefore, DB is a valid alternative to CIE and IF for the detection of antibodies against ENA, Jo-1, and M2 with markedly faster turnaround time. The DB method is also more sensitive for the detection of anti-Scl-70 antibodies.

Table 1. Comparison between DB and CIE for detection of antibodies against SSA, SSB, RNP, SS, Scl-70, or Jo-1, and between DB and IF for detection of antibodies against M2.

<table>
<thead>
<tr>
<th></th>
<th>Concordant</th>
<th>Discordan</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
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<tbody>
<tr>
<td>SSA</td>
<td>126</td>
<td>57</td>
<td>68</td>
<td>1</td>
</tr>
<tr>
<td>SSB</td>
<td>126</td>
<td>98</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>RNP</td>
<td>126</td>
<td>112</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Sm</td>
<td>126</td>
<td>100</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Scl-70</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Jo-1</td>
<td>50</td>
<td>31</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>M2</td>
<td>32</td>
<td>2</td>
<td>28</td>
<td>2</td>
</tr>
</tbody>
</table>

* CIE was considered the reference method for calculation of sensitivity and specificity (including 95% confidence intervals) for SSA, SSB, RNP, Sm, and Jo-1.

Alex Mewis
Godelieve Marien
Norbert Blanckaert
Xavier Bossuyt*

Department of Clinical Pathology
University Hospitals Leuven
Kapucijnenvoer 33
B-3000 Leuven, Belgium

* Author for correspondence. Fax 32 16 332896; e-mail:xavier.bossuyt@uz.kuleuven.ac.be.

Thoughts on After the Genome IV

To the Editor:

The fourth annual After the Genome (ATG) (1) Conference served as a think tank for scientists and visionaries from divergent disciplines who share common visions regarding things to come in biological research as the result of the oncoming flow of genomic information. The wide-ranging presentations addressed topics as diverse as greenhouse warming and unconventional informatic techniques.

My purpose here is not to summarize the different presentations at that meeting, but to present a personal view of how ATG will likely impact clinical diagnostics.

As we all know, a massive frontal attack on both human and non-human genomes is currently underway. Positional cloning, subtractive hybridization, comparative genomic hybridization, expression profiling, high-throughput screening techniques, and protein and other expression systems are all creating massive quantities of data in areas related to structural genomics, functional genomics, and proteomics. Bioinformation systems are therefore rapidly being developed to help integrate and effectively mine this massive amount of information. The express purpose of the entirety of this information is to then aid in our understanding of the genetic basis of disease together with normal and pathogenic biochemical pathways. Because pharmaceutical companies will in turn use this information for identification of possible targets for drug development, the pharmaceutical industry is a primary engine driving this discovery process. Pharmaceutical companies expect that as a direct consequence of ATG, the sum total of different pharmaceutical targets (enzymes, ion channels, receptors, hormones, growth factors, nuclear receptors, DNA, RNA, and unknown targets) will increase by at least one order of magnitude, from 417 to somewhere between 3000 and 10 000 (2). As another direct consequence of ATG, empirical chemical and pharmacological means of drug discovery will be replaced with rational, gene-based therapeutic strategies. This change is expected to increase productivity by decreasing the cost of bringing a registered mole-

References
cul to market and increasing the number of new chemical entities registered each year (3). This also is a major concern for the pharmaceutical industry because research and development costs have increased from $54 million to approximately $600 million per registered molecule during the past 20 years (3).

However, as an indirect consequence of ATG, clinical diagnostics will be forever altered, and there are at least three reasons behind this change: First, one by-product of identifying new targets for drug development is identification of unambiguous genetic and protein markers of disease. After the genome, these new markers will have unparalleled sensitivity and specificity for diagnosing inherited as well as acquired diseases. Furthermore, these markers will be necessary because disease management strategies will be gene-based. In the gene-based era of medicine, diseases will be redefined according their genotype rather than phenotype. Another by-product of drug discovery will be the identification of genetic markers that predispose one to disease. Such predisposition markers will presage the growth of predictive medicine and thereby permit effective screening, early intervention, and disease prevention. Finally, because genetic polymorphisms underlie individual responsiveness to drugs, both the safety and efficacy of drug use will be significantly increased by the use of pharmacogenetics to effectively tailor drug prescriptions to individual genotypes.

What ATG means to clinical diagnostics therefore is becoming clear—many new things to come and the ushering-in of an entirely new season.

References
1. After the genome IV: envisioning biology in the year 2010. 10–14 October 1998; Jackson, WY.

P. Patrick Hess

quest Diagnostics Nichols Institute
33608 Ortega Highway

San Juan Capistrano, CA 92690
Fax 949-728-4930

False-Positive hCG Assay Results Leading to Unnecessary Surgery and Chemotherapy and Needless Occurrences of Diabetes and Coma

To the Editor:

Much concern has been raised by the unraveling at the hCG Reference Service of six cases of persistent phantom human chorionic gonadotropin (hCG). These are false-positive hCG results, which are likely attributable to human anti-mouse IgG or to heterophilic antibodies (1–3). The hCG Reference Service, started in January 1998 to aid with the interpretation of irregular or discordant hCG immunoassay results, requests parallel serum and urine samples. Each is tested in four separate two-step microtiter plate ELISAs (assay 1 detects intact hCG, assay 2 detects non-nicked or bioactive hCG only, assay 3 detects the hCG free β-subunit only, and assay 4 detects the hCG β-core fragment only) at three different concentrations (undiluted, a 1:2 dilution, and a 1:5 dilution). From the data, inferences are made about the nature (nonnicked or nicked hCG, free β-subunit, and β-core fragment) and likely source (trophoblast disease, pituitary hCG, cancer, or phantom hCG) of the hCG immunoreactivity.

In all six cases of phantom hCG tested by the service, increased hCG concentrations were detected in serum samples (Table 1), but no detectable hCG, free β-subunit, or β-core fragment was found in the parallel urine samples (<3 IU/L). In all cases, the presence of phantom hCG was confirmed by at least two of the following three criteria: the finding of serum concentrations that were nonlinear on dilution; the finding of hCG concentrations in a two-step assay that were 20% or less of values in a one-step (single incubation with both coating and tracer antibodies) sandwich assay or that differed by 80% in two different hCG assays; and the finding of measurable β-core fragment immunoreactivity (not usually detectable in serum) in serum samples.

The six cases had similar histories. Each started with an incidental pregnancy test (Table 1). The pregnancy test was positive (69–285 IU/L), and the patient was sent to an obstetrician. In each case, ultrasound failed to reveal a fetal sac, laparoscopy did not reveal an ectopic pregnancy, and dilation and curettage revealed no recent history of pregnancy or trophoblast disease. In each case, the false-positive hCG persisted for an additional 3–11 months (5–451 IU/L) before samples were sent to the hCG

<table>
<thead>
<tr>
<th>Age, years</th>
<th>hCG test</th>
<th>Initial hCG, IU/L</th>
<th>Range of hCG, IU/L</th>
<th>Laparoscopy</th>
<th>Dilation and curettage</th>
<th>Oophorectomy</th>
<th>Hysterectomy</th>
<th>Methotrexate chemotherapy</th>
<th>EMACO chemotherapy</th>
<th>Type 1 diabetes and coma</th>
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<tbody>
<tr>
<td>i</td>
<td>24</td>
<td>hCGβ</td>
<td>117</td>
<td>45–135</td>
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<tr>
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<td>26</td>
<td>hCGβ</td>
<td>52</td>
<td>22–89</td>
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<td>145–351</td>
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<tr>
<td>iv</td>
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<td>78–451</td>
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<tr>
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<td>22</td>
<td>hCGβ</td>
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<tr>
<td>vi</td>
<td>28</td>
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<td>69</td>
<td>48–74</td>
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</tr>
</tbody>
</table>

Table 1. Summary of clinical findings and laboratory data.

a Patients i, ii, and iii are described in more detail in Cole (3).

b Range of hCG concentrations in the 3–11 months (depending on case) after initial detection.