The Paradox in Translational Medicine

To the Editor:
Advances in laboratory sciences have raised expectations of discovery of clinically useful biomarkers, but few such new tests have appeared to date. Hortin et al. (1) highlighted several challenges in the translation of promising markers into clinical laboratory tests. Translational medicine, which is currently defined as the translation of basic research into practical clinical applications, has great potential to develop and deliver new tools that may assist prevention, diagnosis, and treatment of disease (2). In the field of laboratory medicine, the transfer of promising research assays to daily laboratory practice is a challenge that may take several years and involves many sequential processes: development and validation of clinical assays, release of reagents and systems by diagnostic companies, evaluation of the analytical and clinical performances of the commercial assays in the field, and reliable implementation into clinical practice through training laboratory professionals and refining interpretation and utilization of the new information by all medical personnel (3).

Major emphasis is currently placed on uncovering theoretical and methodological difficulties that would explain why only a minority of experimental research has made the transition to the clinical domain and produced new diagnostic tests (1, 4). This inefficiency is attributable not only to obvious and well-recognized drawbacks, such as methodological biases in animal experimentation and differences between animal and human pathophysiology, but also to additional scientific, financial, ethical, regulatory, and practical hurdles (3). Ideally, experimental and clinical research share the same targets of improving disease understanding and cost-effective decision-making. In reality, however, these pursuits frequently evolve through parallel rather than coordinated tracks. Much of the failure in this translation arises from the lack of effective communication between clinicians and researchers; a collaborative rather than competitive relationship between the two groups will be beneficial (3).

Translational investigations typically rely on large research consortiums and population-based plasma banks that couple biomarker information with longitudinal observational data. Basic research, however, usually includes specific hypothesis-driven studies that have small sample sizes and are conducted by independent academic or industry researchers (2). Because of industry support of some basic research in academic institutions, some medical schools, especially the smaller ones, might need to make compromises for fear that companies would suspend funding. Some companies may take ownership of results although academic researchers have generated them. Biased reporting of the clinical benefits of various diagnostic or therapeutic methods may occur because some agreements signed between academic institutions and diagnostic or drug companies require confidentiality of data, often depending on the outcome. As a consequence, negative results may not be emphasized or submitted to medical journals for publication.

Two other problems merit mention. One is the limited funding for developing new diagnostic products in some specific research fields, because industry tends to seek products with a safer return on investment. Finally, there is a serious concern regarding reliability and reproducibility of results because of sample handling; preanalytical variability may influence profiles of some biomarkers. Therefore, the most feasible and standardized collection procedures should be established before results of a novel and promising diagnostic technique such as high-throughput proteomics can be transferred to daily laboratory practice (5).

Few solutions have been proposed to bridge the gap between basic research and clinical and laboratory practice. Accordingly, translational medicine requires reorganization in a thoughtful cooperative manner between basic researchers, clinicians, laboratory professionals, and manufacturers; it should be more clinically driven and supported by funding independent from any potential conflict of interest.

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References

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Primary Hyperoxaluria Remains Undiagnosed in Patients with Hyperoxaluria and Recurrent Urolithiasis

To the Editor:
Primary hyperoxaluria (PH) is a metabolic disorder caused by deficiency
of either the liver-specific enzyme alanine:glyoxylate aminotransferase (AGT) for PH type 1 (PH1) or glyoxylate reductase/hydroxyypyruvate de-hydrogenase (GR/HPR) for PH type 2 (PH2). PH increases endogenous oxalate production, leading to the development of renal stones and nephrocalcinosis, which may result in end-stage renal disease (ESRD) (1). The 1st step in the diagnostic process involves measurement of urinary oxalate, glycolate, and/or l-glycerate, followed by enzymatic analysis of AGT (in liver) or GR/HPR (in lymphocytes), or genetic testing of the AGXT gene for PH1 or the GRHPR gene for PH2. Extensive metabolic screening is rarely performed in adults who present with stone disease because PH disease presentation usually occurs in childhood, not in adulthood. Nevertheless, more than one-third of PH1 is diagnosed in adult patients in the Netherlands (2). Early diagnosis and treatment is of utmost importance in PH, because conservative therapy can prevent renal insufficiency (2), particularly pyridoxine therapy in PH1 (3). If treatment is not initiated in a timely manner, ESRD will ensue in these patients. Therefore, adequate diagnostic measures should be taken after the first clinical signs and symptoms have evolved.

We performed a comprehensive search among all nephrologists in the Netherlands (2) and discovered a relatively high prevalence of PH in the Netherlands. The high number of adult patients who were diagnosed only after the development of ESRD (59% for adults) indicates that our search method may have missed patients with PH and prompted us to design a strategy to identify more patients with PH. During a period of 8 years, in one routine academic hospital laboratory, we traced all patients with hyperoxaluria and performed further metabolic and genetic investigation to diagnose or exclude PH.

Since 1995, urinary oxalate has been measured at the Laboratory for General Clinical Chemistry at the Department of Clinical Chemistry in the Academic Medical Center. Until 2003, results of urinary oxalate screening revealed hyperoxaluria in 32 of 150 patients, according to the reference interval, we determined with a 24-h urine collection study performed in this laboratory. In 25 of these 32 patients (those we were able to contact) we performed analyses of urinary oxalate, glycolate, and l-glycerate in fresh 24-h urine by ion chromatography (Dionex) and gas chromatography. Hyperoxaluria was detected in 6 patients (clinical characteristics as listed in Table 1). One patient had PH1, confirmed by detection of a Gly170Arg mutation on the so-called minor allele of the AGXT gene. The urinary oxalate excretion rate was only mildly increased because this patient used pyridoxine at the time of urinalysis. The other 5 patients had urine glycolate and l-glycerate excretion rates that were within the reference intervals and therefore in these 5 patients the diagnosis of PH was rejected and no further testing was performed. Four of these 5 patients had developed urinary tract symptoms after the onset of intestinal disease, diagnosed as secondary hyperoxaluria related to malabsorption. The 5th patient did not have evidence of PH or secondary hyperoxaluria and therefore this case was classified as idiopathic hyperoxaluria.

In this study, we searched for PH in a specific patient group in which we suspected that PH may have been underdiagnosed (2). Apparently, our strategy led to the discovery of a patient with previously undiagnosed PH. In view of the very low prevalence of PH in populations studied so far, the finding of a new PH patient in a cohort of 150 patients is remarkable and confirms that PH remains undiagnosed in some adult patients, and that the prevalence of this disease may be higher than previously estimated (2). The cases we describe in this report show that PH can be diagnosed only with an immediate and complete diagnostic work-up, a procedure that provides the best opportunity to prevent further renal damage. Therefore, episodes of urolithiasis, nephrocalcinosis, recurrent urinary tract infections, or unexplained decline of renal function require assessment of urinary oxalate to exclude PH. We strongly suggest that performing the same screening strategy in other hospital laboratories will detect more PH patients who may benefit from early recognition and treatment.

As previously reported, hyperoxaluria, dehydration, and other comorbidities may lead to renal involvement (4). Citrate administration decreases the risk of stone formation (5), but this treatment was not used in 3 of the cases we investigated, an omission that may have placed them at higher risk for renal involvement. Therefore, all available conservative measures to decrease the risk of stone formation should be taken in patients with any type of hyperoxaluria.

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Table 1. Characteristics of patients with hyperoxaluria.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at inclusion, years</th>
<th>Age at first symptoms, years</th>
<th>Symptoms</th>
<th>Urinary oxalate, mmol/mol creatinine</th>
<th>Comorbidity</th>
<th>Diagnosis</th>
</tr>
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<tr>
<td>1</td>
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<td>2</td>
<td>UNI⁵</td>
<td>60</td>
<td>SH, SH</td>
<td>PH1</td>
</tr>
<tr>
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<td>34</td>
<td>U</td>
<td>80</td>
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<td>51</td>
<td>UNR</td>
<td>70</td>
<td>Sb</td>
<td>SH</td>
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<tr>
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<td>31</td>
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<td>200</td>
<td>Cd</td>
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<tr>
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<td>48</td>
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<tr>
<td>6</td>
<td>69</td>
<td>50</td>
<td>UE</td>
<td>100</td>
<td>Sb</td>
<td>SH</td>
</tr>
</tbody>
</table>

*Reference value, 0–54 mmol/mol creatinine.

Abbreviations: Symptoms: U, urolithiasis; N, nephrocalcinosis; R, renal insufficiency; I, urinary tract infections; R, renal insufficiency; E, end-stage renal disease; Comorbidity: Sb, short bowel after intestinal resections; Cd, Crohn’s disease; Diagnosis: PH1, primary hyperoxaluria type 1; IH, idiopathic hyperoxaluria; SH, secondary hyperoxaluria.
Quality Assessment of CoaguChek Point-of-Care International Normalized Ratio Monitors: A Note of Caution

To the Editor:

In a recent publication, Poller et al. (1) described quality assessment (QA) of CoaguChek (CUC) point-of-care (POC) international normalized ratio (INR) monitors and compared 2 procedures. The study compared the proportion of 523 CUC monitors having unsatisfactory performance as indicated by either a >15% deviation of INR results from the INR assigned to 5 lyophilized QA plasmas or a >15% deviation from the overall median of INRs obtained on the monitors included in the survey. The INRs assigned to QA plasmas had been derived from a full calibration in compliance with WHO-recommended procedures and a local mean normal prothrombin time.

The CUC device is calibrated by the manufacturer for use with non-anticoagulated whole blood. Patients using the device analyze whole blood and not plasma. Furthermore, the calibration procedure employed by Poller et al. (1) used whole blood samples to derive the International Sensitivity Index for assigning INRs to the lyophilized plasma samples. We believe that caution is required when interpreting data obtained on lyophilized plasma samples for devices calibrated for whole blood, and that results should not be assumed to be representative of results that would have been obtained for whole blood analysis.

We recently reported results for 6 years (1996–2002) of experience with external QA (EQA) of CUC and CUC-S devices, comparing >30 test samples analyzed by up to 175 centers (2). We have continued to perform EQA surveys and recently analyzed data on 8 different freeze-dried plasma samples obtained in 2006 from >800 centers, grouping results according to the lot number of test strips used for analysis. For several hundred test-strip lots used for a series of surveys, no significant difference was observed between results obtained with different lots, with 4 exceptions. On these 4 occasions, results with 1 lot number were >10% different from the median of results with all other lots. For 2 of these lots, test strips were available for further investigation. Native whole blood samples from warfarinized patients were analyzed to assess whether the discrepancy observed in lyophilized plasmas was also present when whole blood samples were analyzed. On the 1st occasion a series of lyophilized plasmas and native (non-anticoagulated) blood samples were analyzed with test strips from 2 different lots, including those for which the lot number was associated with the discrepancy identified in survey data. The whole plasmas and whole blood samples were from different patients. For whole blood analysis, we collected samples by syringe, immediately applied them to strips from both lots, and analyzed them with 2 monitors. The mean INRs with the 2 lots were 3.08 and 3.79 (n = 12, 23% difference, P < 0.001) for lyophilized plasmas. For whole blood, the mean INRs with the 2 lots were 2.75 and 2.96 (n = 10, 8% difference, P < 0.01).

On the 2nd occasion the mean INR of 10 lyophilized National External Quality Assessment Scheme (NEQAS) plasma samples was 3.97 with the lot number under investigation compared to a mean of 3.08 for samples analyzed by NEQAS participants using strips from multiple lots (29% difference, P < 0.001). Native blood samples from 14 patients were analyzed with the lot number under investigation and a 2nd lot number (which survey data had shown to be in agreement with other lots). The mean INRs for whole blood samples were 2.92 and 3.01 (3% difference, not significant) for these 2 lots. Thus the difference present when lyophilized plasmas were analyzed was absent when native whole blood was tested.

The reason for the different results for test strip lots for whole blood and lyophilized plasmas is unknown, but our data indicate that findings based on lyophilized plasma cannot be safely extrapolated to whole blood without supporting evidence.

On the basis of their study results, Poller et al. (1) concluded that a proportion of CUC monitors in current everyday use for dosage control gave unsatisfactory results. Our experience suggests that although this conclusion may be true for lyophilized plasmas, it should not be assumed that the same conclusion applies to whole-blood samples.

We believe that EQA for POC INR devices should be mandatory, as it is for laboratory INR methods. For large multicenter surveys (1, 2), EQA cur-

References

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