and in vivo experiments showed complexation of PSA with inhibitors such as α1-protease inhibitor and protein C (4, 11, 12). A changed glycation of the PSA forms occurs in the presence of prostate carcinoma and could be the reason for the change of the complex formation of PSA with various proteinase inhibitors (13). Thus, these minor PSA complexes produce such concentrations in PCA patients that the above mentioned gap appears. Other possible explanations for these discrepancies between BPH and PCA patients include the calibration of the assays, different recognition of multiple forms of f-PSA or t-PSA in the two groups of patients, and the lack of equimolarity of the tests. However, we believe these rather technical artifacts are ruled out as far as possible by the analytical data described above.

To our knowledge of the literature, this phenomenon was not clearly pointed out until now (3–5, 14). One reason might be that, because of the analytical problems of overestimation mentioned above, the measurement of ACT-PSA concentrations could not be performed reliably in the past (6). When an improved assay for ACT-PSA was used, t-PSA values were frequently greater than the sum of f-PSA plus ACT-PSA, similar to our study (6). However, no additional conclusions were given by these authors.

In conclusion, we believe that our results contradict the high expectations concerning the determination of ACT-PSA or the ratio of ACT-PSA to t-PSA to improve the differentiation between PCa and BPH (15). The f-PSA/t-PSA ratio, and not the ACT-PSA/t-PSA ratio, allowed the best discrimination between BPH and PCa patients. These data correspond to the findings described previously by Björk et al. (14). Other studies also showed that ACT-PSA concentration alone did not improve the specificity for PCA diagnostics over t-PSA (16). Therefore, a recently described PSA immunoassay that detects all complexed PSA forms, such as ACT-PSA, as well as the minor forms except PSA complexed to α2-macroglobulin may eliminate the problem of minor PSA forms as found in our study (17).

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The Value of Screening Inpatients with Creatine Kinase Testing, David Baorto and Mitchell Scott* (Washington University School of Medicine, Division of Laboratory Medicine, Box 8118, 660 S. Euclid Avenue, St. Louis, MO 63110; * author for correspondence: fax 314-362-1461, e-mail mscott@labmed.wustl.edu)

Today's healthcare environment mandates cost-effective utilization of ancillary services, and routine laboratory test panels are often suggested as a target for cost reduction. Over the last 30 years, large multitest profiles have become routine in medical practice and are used to “screen” patients for disease (1, 2), presumably identifying conditions not part of a patient’s clinical presentation (3). However, many studies over the last 20 years have suggested that the use of test profiles provides little benefit toward identification of unknown diseases (4–9). Indeed, it has been suggested that the widespread use of panels was a function of the available continuous flow analyzers (10, 11) and the increased profits afforded lab-
oratories before the establishment of diagnosis-related groups.

Reagent cost savings from elimination of test panels would be trivial in the overall cost of healthcare operations. However, substantial savings might be realized by decreasing the follow-up of slightly “abnormal” results, which yields few new diagnoses (12–14). In the US, the number of “panels” and the number of tests per panel are being minimized to some extent as a result of the new Healthcare Financing Administration-mandated panels and the documentation of medical necessity now required for some forms of reimbursement (15).

We had included a test for total creatine kinase (CK) in a 12-test routine admission panel before May 1, 1996, after which we eliminated several tests from this panel, including CK. One reason for removing CK from this panel was an earlier study that had shown that admission CK tests did not lead to new diagnoses (16). Here we asked whether the prior presence of CK in the panel facilitated the diagnosis of myocardial infarction (MI) for inpatients.

All inpatient admissions to Barnes-Jewish Hospital during the 1-year period before May 1, 1996, were examined. The hospital information system was queried to obtain the following data: admission identifier, admit and discharge dates, associated ICD 9 diagnosis codes, and all CK, CK-MB, and troponin I (TnI) values, all times for test orders and all times for test result entry. The institutional review board approved the data query.

We identified patients whose admission CK may have led to a new diagnosis of MI by identifying admission profiles with an increased CK (>200 U/L), selecting those patients whose first test order time for a CK-MB or TnI followed the result time for the increased total CK within 24 h, further selecting those whose CK-MB or TnI was also increased, and finally selecting those for whom a diagnosis of acute MI was made during the admission. These medical records were reviewed to determine if the increased total CK in the test profile was responsible for the additional work-up that led to the diagnosis of MI. If the CK-MB or TnI order was preceded by classic MI symptoms, an electrocardiogram indicative of acute MI, or other suspicion of MI, it was presumed that the increased CK result did not facilitate the diagnosis of MI and that the CK-MB or TnI would have been ordered anyway. If none of the above three factors was present, the total CK value was considered to have facilitated the diagnosis of MI.

The results of CK, CK-MB, and TnI testing on inpatients during the study period are shown in Fig. 1. There were 38,635 distinct inpatient admissions. Sixty-two percent of these (23,770) had at least one total CK ordered as part of the admission profile 12. Of these 23,770 patients, 7,463 also had at least one CK-MB or TnI ordered.

Twenty-two percent of the inpatients with a total CK in the Profile 12 had at least one value >200 U/L (5,102 patients). Of these, 2,220 patients also had a CK-MB or TnI performed, and 563 had their first CK-MB or TnI ordered after the result time for the increased CK from the profile 12. These 563 represented patients whose screening CK may have triggered the order for the CK-MB or TnI analysis. Of these 563 patients, 183 had a CK-MB or TnI that was increased and 39 of these 183 patients had acute MI as one of their discharge diagnoses. The 39 MI patients had a median maximum percentage of CK-MB that was 5.0% of their total CK value, whereas the 144 non-MI patients with an increased CK-MB had a median maximum CK-MB that was 1.6% of their total CK value. Furthermore, 23 of the 39 MI patients had TnI testing performed, and the median maximum TnI value was 8.5 μg/L. In contrast, 53 of the 144 non-MI patients who had a TnI ordered had a median maximum result below the detection limit of 0.6 μg/L.

Medical records were available for 37 of the 39 patients with MI. In 29 patients, it was clear that the total CK value was not a contributory factor leading to the diagnosis of MI because either a diagnostic electrocardiogram or symptoms of chest pain were noted before the result time for the total CK. In five patients (Table 1, patients 1–5), it was clear that the total CK was contributory from both the timing of results and subsequent orders as well as physician notes. Interestingly, three of these five patients were unable to communicate (Table 1, patients 1–3). Finally, we were unable to determine if the total CK was contributory in three patients (Table 1, patients 5–8) after reviewing the medical records; however, it was interesting that in all three of these patients there was a history of diabetes, a population prone to “silent MI”.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, years</th>
<th>Presenting symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>31</td>
<td>Unconscious, hypoglycemic, renal transplant</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>70</td>
<td>Unconscious, cerebral vascular accident</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>31</td>
<td>Incoherent, disoriented, drug abuse</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>82</td>
<td>Parkinson disease, weight loss</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>77</td>
<td>Dehydration, hepatitis</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>61</td>
<td>Diabetic, shortness of breath</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>71</td>
<td>Diabetic, weakness</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>58</td>
<td>Diabetic, hypoglycemic, renal transplant</td>
</tr>
</tbody>
</table>

Fig. 1. Flow diagram representing selection procedure for patients whose screening CK may have facilitated MI diagnosis.
In summary, of >23 000 admissions with routine CK tests, no more than 8 new diagnoses of MI resulted from the tests. Interestingly, most of the patients in whom the increased total CK was the first clinical clue of an MI were either incapable of communicating or had a history of diabetes, and it is difficult to conclude from the small number whether these subpopulations would benefit from screening.

Of 563 patients who had their first CK-MB or TnI tests ordered following an increased total CK, 67% (380) of these patients never had an abnormal cardiac marker. Our findings would support contentions that unnecessary follow-up testing and evaluations often occur as a result of slightly abnormal values from tests performed as part of a profile (10, 13). Although we cannot determine what percentage of these “more expensive” tests were a direct result of the initially increased CK, it is likely that a large number would not have been ordered without the profile CK result. Taken together with earlier studies, our current findings suggest that limiting the number of tests performed on asymptomatic patients will likely decrease costs across the entire healthcare system, not just the relatively minor direct laboratory costs, with another possible example being orders for bone imaging following slightly increased alkaline phosphatase test results.

The large number of abnormal values in healthy individuals is not completely unexpected. One reason is that reference ranges are defined as the central 95% distribution of healthy subjects, and thus the probability (P) of an abnormal value occurring in a perfectly healthy patient increases with the number of tests (n) performed \[ P = 1 - (0.95)^n \]. Thus, if 12 tests are performed, at least 1 test will be abnormal in 46% of patients. In addition, by their very nature, screening tests are performed on “low-prevalence” populations who are not selected by clinical presentation, which diminishes the positive predictive value (12, 14).

In addition to the frequent use of profiles, many profiles contain redundant tests, thus further increasing the possibility of an abnormal value from a healthy patient. For example, among the following pairs of tests, it is unlikely that the second test provides additional information for most asymptomatic patients: creatinine and blood urea nitrogen, alkaline phosphatase and bilirubin, Na⁺ and Cl⁻, albumin and total protein, alanine aminotransferase and aspartate aminotransferase, and hematocrit and total hemoglobin. Nevertheless, redundant tests like these are still part of the new federally mandated laboratory profiles.

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References

Simple Multiplex PCR for the Simultaneous Detection of the C282Y and H63D Hemochromatosis (HFE) Gene Mutations, Marion K. Stott, Andrew P. Fellowes, Jeff D. Upton, Michael J. Burt, and Peter M. George (Molecular Pathology Laboratory, Canterbury Health Laboratories, P.O. Box 151, Christchurch, New Zealand; *author for correspondence: fax 64 3 364-0545, e-mail pgeorge@chmeds.ac.nz)

Hemochromatosis is a common autosomal recessive disorder of iron metabolism occurring with a prevalence of 0.2–0.5% in Caucasian populations (1–6). The disease is characterized by the excessive accumulation of dietary iron and a progressive rise in body iron stores, which may lead to serious clinical consequences, including cirrhosis, cardiac failure, diabetes, arthritis, and hepatocellular carcinoma. Treatment involves removal of the iron burden by regular venesection and leads to a normal life expectancy if implemented before the development of cirrhosis (7). Thus early detection and treatment are critically important.

Recent identification of a hemochromatosis gene, (HFE, initially termed HLA-H) by Feder et al. (8) allows for early genetic diagnosis and greatly simplifies the screening of a family once affected individuals have been identified. The HFE gene encodes a protein similar in structure to MHC class I-type molecules (9) that interacts with the transferrin receptor to regulate iron absorption (10). Two mutations have been detected in the HFE gene. Most