A multi-test strategy for adrenal tumours

Broadening access to technology and its rapid evolution have transformed clinical care over the past half century. CT and MRI became widely available around 1980, and performance has steadily improved since. Incidental adrenal nodules were detected in only 0·4% of patients undergoing CT scans in the mid to late 1980s, but cross-sectional imaging studies now detect adrenal incidentalomas at least ten times more frequently. In tandem, the refined resolution and the ever increasing imaging volume (3 million in 2018) expose numerous incidental findings, including adrenal nodules. Most adrenal incidentalomas are benign, non-functional adrenocortical adenomas. Adrenal cortical carcinomas (ACCs) are rare, with an overall incidence of only 1–2 cases per million in the general population per year, but they account for roughly 5% of all adrenal incidentalomas. An additional 10–20% of patients with incidentally found adrenal masses display features suspicious for malignancy that cannot be resolved even with modern imaging modalities. ACC is typically highly aggressive, and timely diagnosis and surgical resection have the highest impact on prognosis. Biopsy does not accurately distinguish between benign and malignant adrenal cortical masses and, therefore, patients with suspicious imaging findings are commonly subjected to multiple radiological studies, anxiety, and, for many, potentially unnecessary surgery.

In 2011, Arlt and colleagues reported a retrospective proof-of-principle assessment of urine steroid metabolomics—the combination of mass spectrometry-based steroid profiling with subsequent computational data analysis—as a diagnostic approach for suspicious adrenal incidentalomas. In the extended, international EURINE-ACT validation study, the same group has prospectively assessed this biomarker approach. In The Lancet Diabetes & Endocrinology, Irina Bancos and colleagues describe the use of urine steroid metabolomics to complement imaging in the differential diagnosis of adrenal tumours. With the joint effort of investigators from 14 international centres over 6 years, the EURINE-ACT study included 2017 patients with newly diagnosed adrenal masses, making this the largest prospective study of adrenal incidentalomas so far. The study compared the diagnostic accuracy of initial imaging characteristics of the tumour and urine steroid metabolomics, separately or in combination, with histopathology (where available) or follow-up imaging as the reference standards. As a secondary analysis, they compared the standard CT tumour tissue attenuation threshold of 10 Hounsfield units (HU) with a cutoff of 20 HU. 98 (4·9%) patients were diagnosed as having ACC, all but one of whom had an unenhanced CT scan attenuation >20 HU. Compared with the 10 HU cutoff, using values more than 20 HU sacrificed 1% in sensitivity (100% reduced to 99%) but substantially increased specificity (64% increased to 80%). The authors conclude that the unenhanced CT attenuation cutoff should be raised to more than 20 HU from the 10 HU threshold endorsed by expert guidelines.

A more important finding reported by Bancos and colleagues comes from the use of urine steroid metabolomics. Urine steroid biomarkers were quantified by liquid chromatography-tandem mass spectrometry from 24 h urine specimens collected at diagnosis. A machine learning algorithm classified steroid profiles as indicating low, moderate, or high risk of ACC. The overall positive predictive value of the
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urine steroid metabolomics will require cross-validation this limitation. Furthermore, routine implementation of results by machine learning algorithms partly overcomes clinicians, although the interpretation of complex results, which involve metabolites unfamiliar to most practical considerations relate to the interpretation of availability of instrumentation and expertise. Additional
research to health care has been hampered by scarce availability of instrumentation and expertise. Additional
practical considerations relate to the interpretation of results, which involve metabolites unfamiliar to most clinicians, although the interpretation of complex results by machine learning algorithms partly overcomes this limitation. Furthermore, routine implementation of urine steroid metabolomics will require cross-validation of employed assays against that used to generate the data for the machine learning algorithm to ensure reliable support of clinical decisions. Changes in assays are likely to require updates to computerised algorithms. One possible way to overcome assay variations is the use of cross-validation studies among international laboratories, combined with the use of regionally centralised analysis, which would ensure assay reliability and provide consistent computerised risk classification of steroid profiles.

Bancos and colleagues’ results in the EURINE-ACT validation study open a new set of questions that will need to be addressed by future research and incorporated in practice guidelines. The best approach to patients classified as having intermediate or moderate risk of malignancy needs to be explored. Whether the diagnostic value of steroid metabolomics could be refined by adding analytes or parameters deserves further investigation. Further information is also needed on whether this test can better inform applications of adrenal biopsy in patients with adrenal nodules that can be conclusively diagnosed by histopathology. While the pace of progress in urine steroid metabolomics remains to be determined, the EURINE-ACT study has established the basis for computerised-assisted diagnostics using steroid profiling in adrenal incidentalomas, and it has illustrated the invaluable power of large-scale international collaborations in advancing clinical medicine.

We declare no competing interests.

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