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Potential risk of patient misclassification using a point-of-care testing kit for urine drugs of abuse

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Many commercial kits are available that provide a rapid method to screen for drugs of abuse. The Quantum Diagnostics One-Step Multi-Drug Screen Panel kit (Quantum Diagnostics, Waltham Abbey, Essex EN9 3BZ, UK) is provided for use in a limited number of locations in the authors' hospital to provide a quick screening test for drugs of abuse in urine. Approximately 200 kits are used per year. In the emergency setting, this kit is used as a quick screening method to assess unconscious patients or those who have a head injury or unexplained symptoms where the use of drugs may account for symptoms.[1,2] In the neonatal and maternity unit, the kit is used to monitor babies of mothers who are known to use drugs of abuse, to ensure the health and wellbeing of the baby, which is particularly important when the mother is breast feeding.

A large number of urine dipsticks are available on the market. Most people who perform point-of-care (POC) analysis are familiar with the principle that a positive sample will generate a coloured line, and in a negative sample the coloured line will be absent. However, with the Quantum Diagnostics' screening test[3] the opposite is found, whereby a negative sample will generate a coloured line and a positive sample will not.

As with other drugs-of-abuse screening kits, the Quantum kit is based on a lateral flow chromatographic immunoassay,[3] the results of which are read visually without the aid of any instrumentation. The immunoassay is based on competitive binding, and when a drug is present in the urine sample it competes with the immobilised drug complex for binding to the antibody-coated particles. In the absence of a drug, the antibody-coated particles will bind to the immobilised drug complex and a visible coloured line is produced in the test region on the strip. When a drug is present at a level above the detection limit, it will saturate the binding sites on the coated particles and no coloured line will form in the test region. A second test region acts as a control whereby a coloured line will always be produced if a proper volume of sample has been used, the urine has migrated by capillary flow to the test regions and the appropriate time interval for reading the results is allowed.

As staff only perform the test on an occasional basis, concern was expressed about whether or not users of the Quantum Diagnostics' kits were adequately aware of how the kit operated and were generating accurate results. A short questionnaire was circulated to the six locations in the hospital where the kit is known to be used. Three locations have their own supply (neonatal unit [NNU], delivery suite/maternity ward [MW] and the psychiatric unit [PS]) whereas critical care (CC), the acute assessment unit (AAU) and emergency department (ED) borrow kits as and when required.

The questionnaire covered the interpretation of example test strips and how the test should be performed. Participants were encouraged to complete the questionnaire in the same way they would handle a urine sample. Instructions on how to use the kit and interpret the results were made available with the questionnaire.

It proved difficult to conduct this audit as responses to the questionnaire were not readily forthcoming. Visits were made to senior staff in the different units (in some cases on several occasions) along with telephone calls and reminder letters. A total of 31 responses were received and therefore the data obtained were limited; however, they proved sufficient to cause alarm at the standard of analysis.

Four responses were obtained from staff who had not used the kit: two did not attempt the section concerning interpretation of results and were excluded from the analysis. The other two respondents, who had never used

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Table 1. Responses from individual locations where the Quantum Diagnostics urine kit is in use.

Location	Completed responses	Responses (%)					
		Correct time interval for reading results	Correct identification of negative results	Correct identification of positive results	Correct identification of invalid results	False negative	False positive
ED/AAU	7	29	14	57	50	43	86*
PS	7	43	79	71	86	29	21
NNU/MW	12	75	71	83	79	17†	29‡
CC	3	100	83	100	100	0	17

ED: Emergency department; AAU: Acute assessment unit; PS: Psychiatric unit; NNU: Neonatal unit; MW: Maternity ward; CC: Critical care.

*Includes 36% of answers interpreting a negative result as an invalid response.

†Includes 8% of answers interpreting a positive result as an invalid response.

‡Includes 21% of answers interpreting a negative result as an invalid response.

the urine kit, attempted the questions but 75% of their answers were incorrect. This illustrates how dangerous it is for staff to use a simple urine dipstick without adequate knowledge or training.

Of particular concern is the fact that there does not seem to be a mechanism in place to prevent these staff from performing the urine dipstick test in the clinical setting, despite the availability of a local hospital policy and published guidelines for POC analysis which state that staff must receive adequate training and be certified before providing any POC testing.[4,5]

Point-of-care testing is portrayed as simple, quick and accurate, but it is also recognised that a lack of training or adequate quality assurance can result in potentially serious problems, which clinical governance with active management involvement should eliminate.[6]

Of the 27 responses from users of the Quantum urine kit, only two used it weekly and the majority (52%) used it less than once a month. A considerable proportion of staff (41%) were unaware of the time the strip should be left before reading a result, with some keen to read the strip too quickly and others leaving it for too long. A quarter of staff were unable to identify invalid results and positive results, and 40% were unable to identify negative results. This audit shows that users of the Quantum Diagnostics' urine kit are not performing it to the standard given by the manufacturer in the kit insert.[3]

On closer analysis of the data, there was a marked difference in the number of correct responses obtained from different locations in the hospital (Table 1). In some areas, the results are disturbing, with the majority of staff unable to identify positive or negative samples correctly. In the emergency setting (ED and AAU), where the kit is used on unconscious patients, up to 86% of patients risk being misclassified as drug users when in fact they are not. This could have serious implications in terms of clinical management, in addition to grave social consequences, and could put the trust at a serious risk of litigation. Furthermore, an unconscious patient who has used drugs of abuse has a 43% chance of being classified as free of drugs of abuse (Table 1).

These results highlight a serious clinical governance issue and raise a question about whether or not this kit should continue to be used in the emergency setting. The problem is not with the kit but rather the way in which it is being used incorrectly, leading to a potential misclassification of patients.

At the moment, the Quantum Diagnostics' urine kit is only supplied to NNU, the maternity ward and psychiatric unit in order to limit the use of the kit. However, this audit demonstrates that CC, ED and AAU borrow kits when there is clinical need to exclude or confirm the presence of substances of abuse.

Several possible approaches are available to improve the standard and accuracy of screening urine for drugs of abuse. First, an alternative kit, as there are others on the market that use instrumentation to read the results and thus eliminate operator error in interpreting the results. Second, reducing the number of people eligible to use the kit could result in improved accuracy, as an operator who uses a test on a regular basis is less likely to make errors.

Given that the current approach to limit distribution of kits is ineffective, it was felt necessary to consider whether or not screening for urine drugs of abuse should be performed solely in the laboratory. This proposal was taken to the trust's Patient Safety Committee in order to reduce the risk to patients and improve the quality of the service. As a result, POC testing for drugs of abuse is no longer available and the laboratory is providing this service using a Chirus instrument (Chirus, Watford, Hertfordshire WD18 8PH, UK). The use of such an instrument by qualified biomedical scientists eliminates operator error, provides a printout and a report that can be filed in the pathology IT system.

This study provides a clear illustration of the dangers of POC analysis where it is undertaken by staff not adequately trained or who lack suitable knowledge and experience. In some areas of the hospital there was a high probability that patients risked being misclassified, which could lead to serious consequences for patient management. As a result, a recommendation to abandon the provision of POC analysis for drugs of abuse, to be replaced by a service provided by the laboratory, was accepted and implemented by the trust. □

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No evidence for *JAK2* V617F mutation in colorectal cancer

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Colorectal cancer (CRC) is the third most common cancer and the fourth most common cancer cause of death globally,[1] and 40–50% of newly diagnosed patients will develop metastatic disease.[2] Despite therapeutic advances, the prognosis for patients with metastatic CRC remains poor, with a median overall survival of 18–21 months.[3]

The Janus family of tyrosine kinase 2 (JAK2) and the signal transducers and activators of transcription (STAT) family of transcription factors are crucial components of diverse signal transduction pathways that are actively involved in cellular survival, proliferation, differentiation and apoptosis.[4] JAK2 is constitutively associated with many cytokines and is responsible for signalling from various growth factor receptors, and this mutation results in deregulated intracellular signalling with cell proliferation that is independent of normal growth factor control in different types of malignancy.[5]

A somatic point mutation (V617) has been described in the conserved autoinhibitory pseudokinase domain of JAK2 protein, which plays an important role in haematopoietic signalling and in myeloproliferative disorders such as clonal polycythaemia vera, essential thrombocythopenia[6] and chronic idiopathic myelofibrosis.[7] In this V617 mutation, the G→T exchange at nucleotide 1849 in exon 12 of the *JAK2* gene leads to a substitution of valine to phenylalanine at amino acid position 617 of the JAK2 protein within the JH2 pseudokinase domain.[8] This conformational change promotes the constitutive (trans)-phosphorylation of activation loop Y1007 and constitutive kinase activity, although the mutant JAK2 retains its ability to bind the cytosolic domains of cytokine receptors[9] and requires binding dimeric cytokine receptors for full activation. *JAK2* V617F activates multiple signalling pathways that function downstream of the wild-type *JAK2*, such as the STAT3, STAT5, RAS/MAPK and PI3K-Akt pathways.[10]

The Ras/Raf/MAPK and PI3K/Akt pathways are immediately downstream of epidermal growth factor receptors (EGFR) and have been analysed in solid tumours, especially in CRC, as they converge to drive proliferation, survival, angiogenesis, metastasis and invasion. It is also well known that metastatic CRCs respond differently to EGFR-targeted agents and that the tumour-specific response has a genetic basis.

As a consequence, a great deal of recent works has defined mutations in genes included in this pathways as *KRAS* (human homolog of the Kirsten rat sarcoma-2 virus oncogene), *BRAF* (V-raf murine sarcoma viral oncogene homolog B1) and phosphatidylinositol 3-kinase (PI3K) events distinguish malignant from normal cells and make tumours resistant to treatment with anti-EGFR monoclonal antibodies such as cetuximab or panitumumab.[11,12] Despite extensive study, there are patients with wild-type *KRAS, BRAF* and PI3K who do not respond to these treatments. In contrast, *JAK2* mutations have not been studied in solid tumours, including CRC.

Corvinus *et al*.[13] showed that persistent STAT3 activation in CRC is associated with enhanced cell proliferation and tumour growth, and the blockade of STAT3 activation in CRC-derived xenograft tumours slowed their development. In addition, studies in cell lines showed that JAK2 interacted functionally with Raf-1, a central component of the RAS/MAPK pathway. Therefore, it is possible that the *JAK2* V617F mutation may lead to disruption of one or more of these pathways, influencing normal cellular responses and resulting in different disease states in CRC. The role of JAK-STAT mutations in cancer is being explored and it is possible that mutations in components of this pathway are present in various cancers, including CRC.[14]

The identification of this acquired mutation establishes the presence or absence of a clonal disorder and would allow better or new approaches to the diagnosis and treatment of this type of tumour.

Table 1. Patient demographics and baseline tumour characteristics.

Gender	Male	70.8%
	Female	29.2%
Age	Median (range)	68 years (31–88)
Duke's stage	A	10.7%
	B	12%
	C	70.6%
	D	6.7%
Histological Grade	Well differentiated	4.6%
	Moderately differentiated	81.6%
	Poorly differentiated	13.8%

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