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THE ROLE OF CLINICAL LABORATORIES IN PERSONALIZED HEALTHCARE
EDITORIAL

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Guest Editor

It seems incredible to think that it is now 14 years since the turn of the millennium and the announcement of a 'rough draft' of the human genome. Alongside developments in molecular biology and diagnostic techniques, this provided the promise of an exponential increase in the amount of information that physicians could call upon in their decision making, and made the idea that individual patients could have their therapy 'tailored' to provide the best chance of an optimal outcome a real possibility. Indeed, as we enter 2014, the traditional 'one size fits all' approach to drug administration is being increasingly replaced by a much more specific and tailored approach, termed 'personalized healthcare' (PHC) [1, 2].

Several compelling reasons make it clear why we now need to think about healthcare in terms of an individualized approach. For example, it has become increasingly apparent that there is substantial inter-individual variability in the absorption, metabolism and excretion of drugs which impact both efficacy and safety. Adverse drug reactions account for approximately 100,000 deaths, 2 million hospitalizations, and have an associated cost of US$100 billion every year in the USA alone [3–5]: PHC may allow us to reduce this burden through appropriate adjustment of drug therapy in those patients identified as at risk of such events. Similarly, there is an increasing appreciation of how heterogeneous a disease once considered a single entity may be. The classification of breast cancer, for example, has undergone continual refinement as the role of factors such as estrogen receptor, human epidermal growth factor receptor (HER2), and Ki67 status has become understood [6], with corresponding implications for the selection of appropriate treatment. Our evolving understanding of disease has also gone some way to explaining the observation that our medicines often fail to display the same efficacy in real-world clinical settings as that seen in randomized trials [7].

A cornerstone of PHC is the development of reliable diagnostic assays, capable of identifying pharmacogenetic traits that stratify patients into groups proven to experience different outcomes if treated with the same drug. Appropriate integration of such testing can enable the stratification of disease status, selection of the correct medication, and/or the tailoring of drug dosages to that patient's specific needs. Indeed, pharmacogenetic testing to inform drug selection and dosing is now routine in many settings and has been particularly successful in oncology: of 158 US Food and Drug Administration (FDA)-approved drugs containing pharmacogenomic information, about one-third of these are used in oncology [8]. A breast cancer biopsy that tests positive for expression of the growth factor receptor HER2 has been a requirement for treatment with trastuzumab (marketed as Herceptin®) ever since the FDA approved the drug in 1998 [9]. Another prominent example is the routine use of epidermal growth factor receptor (EGFR) expression and KRAS mutation testing in colorectal cancer patient biopsies prior to the use of the anti-EGFR monoclonal antibody therapies cetuximab and panitumumab [10, 11].

Partly in response to the high failure rate of new drug candidates and the escalating research and development costs experienced by the pharmaceutical industry, the development of a 'companion' diagnostic test alongside clinical development of targeted therapies is now considered essential. It is hoped that clearly identifying the subgroup of patients with the greatest likelihood of benefitting from treatment as early as possible in product development will speed up development and maximize the chances of clinical success. Indeed, this approach proved highly successful during the development of vemurafenib (Zelboraf®) for metastatic melanoma. The BRAFV600 mutation is present in around 50% of melanomas [12], and vemurafenib only works in those patients with this mutation. The early development of a companion diagnostic test for the BRAFV600 mutation was therefore essential to identify eligible patients for inclusion in clinical trials. More recently, we've seen these benefits apply to non-small cell lung cancer, with crizotinib (Xalkori®) and the anaplastic lymphoma kinase (ALK) re-arrangement [13]. As we move forward, it is likely that the results from diagnostic assays will increasingly determine the appropriate choice and dose of drug

in an individual patient. This will mean that the tests performed in clinical laboratories assume an even greater significance within the healthcare system.

Recognizing the critical role of the clinical laboratorian in supporting the continuing evolution of PHC, this special issue of the eJIFCC is dedicated to discussing progress in the field, highlighting some of the challenges and success stories, as well as speculating on some exciting future applications of the concept. Within this edition's content are articles highlighting that routine diagnostic testing to inform drug selection/drug dosing is not limited to oncology. The achievements and challenges of implementing pharmacogenetic testing are highlighted with some recent data. In cardiovascular disease, for example, the use of NT-proBNP-guided therapy management has been associated with improved outcomes and quality of life in heart failure patients [14], and platelet function-guided therapy now forms part of clinical guidelines for percutaneous coronary intervention [15]. Also discussed in several articles in this issue are examples of the many areas of great unmet need in which molecular testing holds huge promise. For example, assays capable of identifying subjects at high risk of progression to Alzheimer's disease – a group who in future may be eligible for early treatment, when the chances of delaying disease progression may be greatest – are of significant interest, particularly given our aging population [16]. Advances in our understanding of the molecular basis of asthma may, at least in part, explain the heterogeneity in response to medication seen. For patients with this disease – in whom exacerbations can still be life threatening – laboratory testing also has the potential to allow tailoring of treatment based on individual characteristics, and to improve overall treatment success [17]. Alongside the promising advances in PHC described in this issue, there has been, and will continue to be, a corresponding increase in the role of clinical biochemistry laboratories in supporting evidence-based clinical decision making. This issue also provides an overview of the EuroMedLab satellite symposium that provides an important forum for education and discussion of all the issues that are raised through the increasing use of PHC.

It is clear that the growing number of game-changing targeted therapies in development will require ever more innovative diagnostic tools to guide their use. It is envisaged that clinical laboratories will, therefore, play an increasingly pivotal role in the future, with clinical scientists uniquely placed to ensure that the opportunities afforded by personalized medicine can be maximized, thus supporting improved patient outcomes.

References

1. Creeden J. Building bridges to the future of medicine: recommendations for boosting development of novel and companion diagnostics. Pharmacogenomics. 2012; 13(14):1651–1659.
2. Desiere F, Gutjahr TS, Rohr U-P. Developing companion diagnostics for delivering personalised medicine: opportunities and challenges. Drug Discov Today Ther Strategies 2013; in press. doi:10.1016/j.ddstr.2013.05.002.
3. Lesko LJ, Zineh I. DNA, drugs and chariots: on a decade of pharmacogenomics at the US FDA. Pharmacogenomics. 2010; 11(4):507–512.
4. Davies EC, Green CF, Taylor S, Williamson PR, Mottram DR, Pirmohamed M. Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. PLoS One. 2009; 4(2):e4439.
5. Wilke RA, Lin DW, Roden DM, Watkins PB, Flockhart D, Zineh I, et al. Identifying genetic risk factors for serious adverse drug reactions: current progress and challenges. Nat Rev Drug Discov. 2007; 6(11):904–916.
6. Senkus E, Kyriakides S, Penault-Llorca F, Poortmans P, Thompson A, Zackrisson S, et al. Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment, and follow-up. Ann Oncol. 2013; 24(Suppl 6):vi1–vi23.
7. Spear BB, Heath-Chiozzi M, Huff J. Clinical application of pharmacogenetics. Trends Mol Med. 2001; 7(5):201–204.
8. US Food and Drug Administration. Table of pharmacogenomic biomarkers in drug labeling. Available at: http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm (last accessed January 2014).
9. Herceptin (trastuzumab) US prescribing information. Genentech, November 2013. Available at: http://www.gene.com/download/pdf/herceptin_prescribing.pdf (last accessed January 2014).
10. Erbitux (cetuximab) US prescribing information. Bristol-Myers Squibb, August 2013. Available at: http://packageinserts.bms.com/pi/pi_erbitux.pdf (last accessed January 2014).
11. Vectibix (panitumumab) US prescribing information. Amgen Inc., March 2013. Available at: http://pi.amgen.com/united_states/vectibix/vectibix_pi.pdf (last accessed January 2014).
12. Wagle N, Emery C, Berger M, Davis MJ, Sawyer A, Pochanard P, et al. Dissecting therapeutic resistance to RAF inhibition in melanoma by tumor genomic profiling. J Clin Oncol. 2011; 29(22):3085–3096.
13. Shaw AT, Kim D-W, Nakagawa K, Seto T, Crinó L, Ahn M-J, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med. 2013; 368(25);2385–2394.
14. Januzzi JL, Rehman SU, Mohammed AA, Bhardwaj A, Barajas L, Barajas J, et al. Use of amino-terminal pro-B-type natriuretic peptide to guide outpatient therapy of patients with chronic left ventricular systolic dysfunction. J Am Coll Cardiol. 2011; 58(18):1881–1889.
15. Aradi D, Storey RF, Komócsi A, Trenk D, Gulba D, Kiss RG, et al. Expert position paper on the role of platelet function testing in patients undergoing percutaneous coronary intervention. Eur Heart J. 2014; 35(4):209–215.
16. Blennow K, Hampel H, Weiner M, Zetterberg H. Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. Nat Rev Neurol. 2010; 6(3):131–144.
17. Portelli M, Sayers I. Genetic basis for personalized medicine in asthma. Expert Rev Respir Med. 2012; 6(2):223–236.