Incidental germline variants in 1000 advanced cancers on prospective somatic genomic profiling protocol

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Editorial

The field of cancer genomics and our understanding of tumour biology has progressed rapidly in recent years and position papers regarding genomics-driven cancer medicine have been published by both American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO).[1 2]

Molecular profiling has been increasingly implemented in predicting response to therapy and identifying potential molecular targets in tumour cells for targeted cancer treatments, such as protein kinase inhibitors and monoclonal antibodies. There has been rapid development of molecular profiling with availability from both commercial and academic providers. Molecular profiling has also evolved from single-gene assays, to massively parallel DNA sequencing, also known as Next-Generation Sequencing (NGS).[3-5]

The growing utilisation of NGS poses a challenge with how to properly interpret the vast output of data, merge with existing knowledge, and translate it into valid therapeutic decisions.[6 7] Currently, there is low genomic confidence in NGS testing and clinical application amongst physicians, however the outlook on incorporating NGS technology into clinical practice is positive.[8 9] To reinforce the use of NGS profiling in clinical practice, there is a strong need for careful analysis of NGS results done on individual basis, assessing the legitimacy and usefulness of the data in the context of the patient.

In this *Journal* Meric-Bernstam et al. studied the role of incidental findings of pathogenic germline variants (PGVs) in 1000 patients who underwent somatic mutation screening as part of an established research protocol at MD Anderson [REF]. The focus of this analysis was a) to establish the percentage of PGVs in a general cancer population who underwent somatic mutation testing, b) to address how relevant such PGVs were by cross-referencing established databases and confirming those with an orthogonal CLIA platform, and finally c) to feedback relevant results back to patients by offering genetic counselling. PGVs were identified in 43 of the 1000 patients of which 23 (2.3%) were previously unrecognised – the remaining 20 variants were previously known. Results of the 23 patients were discussed in a 'Return of Incidental Result Committee' where consensus of the

relevance was obtained and subsequently approached for genetic counselling - at the time of analysis 7 patients went through genetic counselling.

The authors addressed a relevant issue of day-to-day cancer mutation testing, namely the handling and reporting of PGVs. Increasingly with larger gene panels in use clinicians and molecular pathology laboratories are faced with this issue. In a pragmatic and elegant way the authors addressed this issue and combined two ongoing protocols, a) General somatic cancer mutation analysis protocol and b) Incidental Germline Results protocol which ultimately allowed the research team to feedback PGV results to patients/families. Although the overall incidence of PGVs was low, in 7 patients genetic counselling was offered. The authors recognised that their approach had some relevant flaws, i.e. 19 of 56 genes covered as recommended by ACMG - important 'familial cancer syndrome genes' such as CDK4 and CDKN2A were not covered; several patients with very advanced cancers passed away throughout the testing process; it was also not clear whether any counselling resulted in wider action in subsequent family members. However the overall strength of this study was to address the relevant issue of PGV reporting and to establish a framework on how results can be validated and communicated with clinical teams and ultimately shared with patients and families. This pragmatic approach could conceptually be the basis of an improved reporting system for PVGs across the research and clinical community.

More importantly, such a framework would entail:

- Consent patient
- Educate physicians and communicate professionally; returning genetic results by proposing a design for a qualified disclosure policy
- Offer counselling where appropriate; balance advantages and drawbacks of sharing genetic data with patients and relatives
- Offer Genomics review Board/MDTs; quality aspects

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