Bridging the gaps between cancer genomics, computational solutions and healthcare delivery

Abstract (89 words)

For learnings from academic research to impact health outcomes, they must be embedded into routine clinical practice. Research innovations such as the human genome project, next-generation sequencing technology and the International Cancer Genome Consortium (ICGC) have provided a wealth of knowledge describing the contribution of the genome to cancer development, disease behaviour, treatment response and clinical outcome. These learnings have the potential to improve survival for cancer patients. Realisation of this potential requires bridging of the translation gap to unlock the clinical, as well as the biological, meaning of genomics.

Main text (1,287 words)

Precision medicine is the matching of individual patients to treatments that maximise therapeutic benefit. Genomics, alongside transcriptomics, epigenetics and other 'omics, is a key enabler of this process. Advances in genomics to date have largely been restricted to a single-gene single-drug paradigm, as exemplified by EGFR inhibitor therapy for *EGFR*-mutant lung cancers. Unlocking the true power of genomics requires integration of comprehensive genomic profiling with clinical and outcome data to build datasets comprising many thousands, if not millions, of patients, thus providing a platform for leveraging artificial intelligence-driven analytics.

Comprehensive genomic profiling - the identification and integrated analysis of all relevant genomic features in a cancer - has demonstrated utility in disease classification, prognosis, and prediction of both treatment response and patient outcomes. Early examples from haemato-oncology highlight this potential of genomics to impact patient care in myriad ways. Diffuse large B-cell lymphoma, the most common haematological cancer, can be split into subtypes with different genomic profiles and clinical outcomes, suggesting benefits from differentiated treatment strategies [1]. Genomics-based classification of myeloproliferative neoplasms improves outcome prediction and facilitates patient-tailored therapy [2]. In acute myeloid leukaemia, models trained on knowledge banks of thousands of patients' data can predict the likelihood of disease remission and better identify those benefitting from stem cell transplantation versus consolidation chemotherapy [3]. These scenarios are driving a shift in haemato-oncology from the historical phenotype-based approaches to patient management to genomics-based treatment algorithms. Recent studies in breast, prostate and colorectal tumours demonstrate similar predictive and prognostic significance of genomic data in solid tumours, as well as highlighting how co-occurrence of genomic drivers impacts tumour behaviour [4–6].

Whilst the majority of clinical studies to date have focussed on analysis of coding variants in a limited number of genes [7], a recent study integrated comprehensive multi-parameter genomic profiling with clinical outcomes to predict treatment response in testicular cancer [8]. This work highlights a pressing need for large projects in other cancer types which integrate all cancer-relevant genomic variants with key clinical outcomes. Accumulating

evidence indicates that genomic data need to be comprehensive for both variant type (copy number, structural variants, genomic signatures etc) and genomic feature type (splicing, regulatory etc) in order to train classifiers and fully unlock clinical utility. The current lack of large solid tumour genomic datasets with associated clinical data is creating a chicken-and-egg scenario, where the utility and evidence around the benefits of comprehensive molecular profiling for cancer patients is both required for, and yet can only be generated by, widespread clinical adoption. Only the adoption of comprehensive genomic profiling into healthcare systems (and eventually global integration of data) will generate enough multi-dimensional data from sufficient patients to power substantial progress within our generation, yet healthcare systems often only adopt genomic profiling once there is evidence of immediate clinical utility to justify the cost.

International research efforts have identified around 600 genomic drivers that are relevant to cancer development, diagnosis, prognosis or response prediction [9]. While some genes, such as *TP53*, are mutated in a large proportion of tumours, many cancer drivers are found in only a few percent of cases. Cancers typically harbour 4-5 driver variants each [9], giving rise to almost limitless combinations of drivers, both within cancer types and between the 200 or so different cancers currently recognised [10]. This variability means that thousands or tens of thousands of cases are needed per cancer type, to identify, and power analyses of the prognostic effect of, low frequency cancer genes, or to predict differences in outcome with sufficient confidence and precision to support clinical decision making. The complexity of cancer biology and genomics explains why a one-size-fits-all approach to treatment fails to deliver benefits for many individuals and makes the case for a move towards a precision medicine approach, where biomarkers are used to match patients to appropriate therapies.

Powering the clinical trials needed to assess precision therapeutics again requires many thousands of cancer patients with genomic data and progress is painfully slow with current strategies for obtaining this. Since comprehensive genomic profiling is not currently standard of care for most cancers or in most healthcare systems, trials of biomarker-directed therapeutics face a major challenge in finding patients. There were over 700 cancer drugs in late phase clinical trials in 2017, with a third of clinical trials using biomarker stratification [11]. For a cancer with the prevalence of pancreatic cancer - circa 10,000 cases per year in the UK - it would take 2 years and around $1.4 million in screening costs, using commercially available genomic assays, to find enough patients for a phase 1 trial using a biomarker with 10% prevalence given typical clinical trial recruitment rates. This time and effort severely limits the number of conventional clinical trials that can be run and contributes to the spiralling costs of those drugs that do ultimately gain approval. A very large number of such trials is required to test all new cancer drugs with genomic biomarkers, along with the exponential number of drug combinations and scheduling/dosing strategies.

We are currently at an impasse: academic researchers are moving away from molecular characterisation of cancers, with the focus shifting instead to prevention and early detection; industry is struggling to find adequate patients to power precision medicine drug trials; and healthcare systems are often choosing to implement limited scope tests covering small numbers of biomarkers rather than commissioning comprehensive genomic profiling.

While current clinical utility alone may not be sufficient to justify the routine use of comprehensive genomic profiling, this approach delivers a multitude of additional benefits by enabling self-learning healthcare systems [12]. A self-learning healthcare system is one that uses the data it generates to feed back into a cycle of continual updating and improvement. Deploying comprehensive genomic profiling for all patients as standard of care is the fastest way to generate real-world clinical-genomic datasets of sufficient size to power the self-learning process. Such datasets can be leveraged to develop the knowledge bases and artificial intelligence-powered statistical models that have already demonstrated utility in haematological malignancies. These learnings can then, in turn, shape clinical guidelines and routine oncology practice. Delivery within public healthcare systems would ensure the data is owned by patients and their doctors. This would facilitate data sharing/aggregation and prevent the fracturing of data into small underpowered siloes, whilst still enabling academic research and revenue-generating commercial access from the soon-to-be $504 billion digital health sector [13].

Comprehensive genomic profiling of all cancer patients would, in effect, turn the entire oncology patient population into a platform trial by providing a surrogate master protocol with molecular screening. This would reduce the set-up time, patient recruitment time and costs for trials of biomarker-driven therapies and hence accelerate therapeutic development. While clinical trials may historically have been seen as research rather than healthcare, they are the only therapeutic option for many patients with advanced cancer and are increasingly viewed as a desirable part of routine management [14,15]. The vast majority of those living with cancer are willing to participate in a clinical trial [16]. In addition, commercially sponsored clinical trials are revenue generating for public healthcare systems, delivering an average return of £6,658 ($8,587) per patient [17] alongside an average pharmacy saving of £5,250 ($6,771).

At present, the lack of large datasets integrating comprehensive genomic profiling with treatment response and clinical outcomes is a significant roadblock in the path to unlocking the full clinical utility of genomics in cancer. Deploying comprehensive genomic profiling for cancer patients removes this impasse and provides a win-win-win for healthcare systems, drug developers and patients. The first healthcare system to successfully deliver genomic data and clinical data in secure and interoperable formats will reap the largest rewards, both from the investment it will attract, the development opportunities it will provide, and by supplying a state-of-the-art service for their patients.

Funding statement
None

Declaration of Interest
PAB provides consultancy on cancer genomics and drug development for Karus Therapeutics, OncoDNA and Cambridge Cancer Genomics. SLC declares no conflict of interest.

References

[1] Lacy SE et al. Blood. 2020 May 14;135(20):1759-1771.
[2] Grinfeld J et al. N Engl J Med. 2018 Oct 11;379(15):1416-1430.
[3] Gerstung M et al. Nat Genet. 2017 Mar;49(3):332-340.
[4] Nyquist MD et al. Cell Rep. 2020 May 26;31(8):107669.
[5] Datta J et al. Clin Cancer Res. 2020 Mar 1;26(5):1077-1085.
[6] Costa C et al. Cancer Discov. 2020 Jan;10(1):72-85.
[7] Available from: www.aacr.org/professionals/research/aacr-project-genie/
[8] Loveday C et al. Nat Commun. 2020 May 4;11(1):2189. *An integrated analysis of all types of genomic variants in testicular cancer.
[9] The ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium. Nature 578, 82–93 (2020).
[10] Available from: www.cancerresearchuk.org/about-cancer/what-is-cancer
[11] Global Oncology Trends 2018: Innovation, Expansion and Disruption. IQVIA Institute for Human Data Science, May 2018.
[12] Foley & Vale. Learn Health Sys. 2017 May 31;1(4):e10025.
[13] Available from: www.gminsights.com/pressrelease/digital-health-market
[14] Fiore LD et al. N Engl J Med. 2016 Jun 2;374(22):2152-8.
[15] Weber JS et al. J Clin Oncol. 2017 Jan 10;35(2):139-140. **An important discussion of the role of early phase trials as an option for advanced cancer patients.
[16] Moorcraft SY et al. Trials. 2016 Jan 9;17:17.
[17] Available from: www.nihr.ac.uk/documents/impact-and-value-report/21427