The road to precision oncology

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The goal of precision medicine is to use population based molecular, clinical and other data to make individually-tailored clinical decisions for patients, though the path to achieving this goal is not entirely clear. A new study shows how knowledge banks of patient data can be used to make individual treatment decisions in acute myeloid leukemia.

Our understanding of the molecular diversity of disease is increasing dramatically, and unveiling vast complexity. The longstanding premise that diseases that appear morphologically similar or even identical are underpinned by similar molecular and genetic abnormalities has proven to be incorrect. As a consequence, developing therapies that target specific molecular processes for these diseases is becoming more and more challenging as ever increasing sub-groups of diminishing size are replacing what was previously a single disease entity. This perhaps explains why many potential therapies have failed particularly in cancer, and why many current therapies are only effective in sub-groups that cannot be predicted prior to treatment. Given these challenges, how do we approach the treatment of disease with what is now variably termed precision, personalised, individualised, or stratified medicine? On page XXX of this issue, Peter Campbell, Hartmut Döhner and colleagues present one potential approach for making individualized clinical care decisions in the treatment of acute myeloid leukemia (AML) patients[1]. The approach leverages information from a large number of AML patients in order to predict the best treatment for an individual patient.

The knowledge bank approach

At first observation, this approach may appear obvious: accumulate a knowledge base—often referred to as a knowledge bank—that captures the clinical features and the molecular pathology of diseases of many patients, ideally within a health system environment to guide optimal treatment choices. The end goal of such a strategy is to enable what is referred to as a self-learning health system, where accrued data informs ongoing development of interventions and processes. Based on this concept, many large-scale efforts have been initiated including the 100,000 Genomes Project in the UK[2], the Precision Medicine Initiative in the United States[3] and the Global Alliance for Genomics and Health[4], as well as many others across the globe.

The central belief is that having these data together will allow us to make better informed choices with regard to individual patients. However, the mechanism as to how we make these treatment decisions in a robust way, the metrics, parameters and statistics that will be required are yet to be established. The article by Gerstung *et al.*[1] is perhaps the first description of how a knowledge bank approach can, and potentially should be used to inform clinical decisions. In this case, the article explores the knowledge bank idea in the context of AML. Treatment

of this disease has advanced dramatically over the last several decades, and central to the treatment is the requirement for a bone marrow transplant. Whilst effective, bone marrow transplantation is not without significant morbidity and potential mortality, and has a substantial cost implication.

The authors show that by compiling the genetic, clinical and molecular attributes for individual patients they can cluster them into sub-groups where more informed decisions can be made about an individual's treatment choice **(Figure 1)**. Perhaps the most challenging question concerning transplantation in AML is whether or not to transplant at first remission after induction chemotherapy. Patients who are in remission can either receive consolidation chemotherapy or a bone marrow transplant. There are currently no means to determine which path is optimal for each patient. Using the knowledge bank as presented by Gertsung *et al.*, 20-25% of patients have the option of chemotherapy rather than transplantation with the same overall long-term outcome. This is an important decision as transplantation is associated with a 20% mortality risk and increased morbidity.

Moving knowledge to the clinic

Whilst knowledge banks containing large numbers will be important, the numbers required to address current key clinical questions are not staggeringly large. The study by Gertsung *et al.* reports on 1,540 patients, with the dramatic findings that almost a quarter of patients can have their therapy decision changed based on this knowledge bank approach. Of course, as we delve into smaller and smaller clinically relevant subgroups, the numbers will need to increase. However, the ability to dramatically inform treatment decisions as the authors demonstrate, with considerable benefits in morbidity and mortality, and substantial potential cost savings epitomize the goals of precision oncology.

Some may reasonably argue that we have always used a knowledge bank approach in clinical medicine. That knowledge bank resides within the experienced clinician who takes information from various sources, most of which imperfectly reflects the clinical scenario of the patient in front of them, and synthesise the information to make a treatment decision. This "clinical judgement" is based on an individual's experience and knowledge base, which the "knowledge banks" of the future aim to enhance.

As demonstrated by Gertsung *et al.* we can refine current therapeutic choices for available therapies using a knowledge bank approach. This then raises the question as to whether the data reported here are ready to be used in the clinic as part of routine practice. In the current environment, the answer is no, and a randomised, appropriately controlled study is feasible to address this question and further validate the selection model prior to implementation. Yet if the ultimate goal is to use knowledge banks to improve healthcare, and we are faced with ever increasing diversity and complexity of disease, data emerging from larger knowledge banks may not be tractable to test using traditional clinical trial designs. Defining quality standards, particularly for clinical data and metrics around what is considered to be an effective intervention, and the path to broader implementation and regulatory approval will be vital if we are to effectively realise the promise of knowledge banks for clinical medicine.

References

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2. Marx, V. *Nature* **524**, 503–505 (2015).
3. Collins, F.S. & Varmus, H. *N. Engl. J. Med.* **372**, 793–795 (2015).
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Figure 1. The knowledge bank approach. A knowledge Bank accrues information from parameters that are relevant to the disease and its treatment permitting novel generalizable insights about the disease and its subgroups. An individual patient's specific characteristics are reflected upon the knowledge bank to define an individual's risk profile for different treatment choices. As the number of participants in the knowledge bank grows, the confidence with which predictions for individual patients continuously grows. The sediment plots show the risk of each outcome over time for each treatment choice.