The future of precision medicine: towards a more predictive personalized medicine

Olivier Elemento

Caryl and Israel Englander Institute for Precision Medicine, Weill Cornell Medicine, New York, NY 10021, U.S.A

Correspondence: Olivier Elemento (ole2001@med.cornell.edu)

Precision medicine can be defined as personalized medicine enhanced by technology. In the past, medicine has, in some cases, been personalized. For example, some drugs are dosed on an individualized basis based on age, body-mass index, comorbidities and other clinical parameters. However, overall, medicine has largely followed the ‘one-size-fits-all’ paradigm as exemplified in the treatment of essential hypertension or type 2 diabetes mellitus. What has changed in the past few years is that technologies such as high throughput sequencing, mass spectrometry, microfluidics, and imaging can help conduct a multitude of complex measurements on clinical samples. Aided by analytics, these technologies have been providing an increasingly detailed picture of molecular and cellular alterations underlying numerous diseases and have revealed tremendous variability between individuals and patients at the molecular and cellular level. These findings have motivated a more personalized or ‘precision’ approach to medicine, in which molecular and cellular markers help tailor patient management to each individual. Here we provide an overview of the key factors driving adoption of precision medicine and highlight current research that may soon make precision medicine more predictive.

It is important to distinguish the practice of precision medicine from precision medicine research. Precision medicine research seeks to identify quantifiable markers that reliably predict a phenotype, such as response to a specific therapy. Markers may be simple such as individual genetic polymorphism or complex such as expression of multiple genes, presence of multiple inherited genetic variants and the product of an algorithm that combines multiple markers. Once markers are identified and validated, typically in one or more individual patient cohorts and often prospectively, they can be used to predict a phenotype in individuals. This latter process is called precision medicine.

Remarkable achievements in precision medicine have occurred in the past few years. A multitude of FDA approved drugs have pharmacogenomic labels [1], meaning a genomic biomarker can predict their efficacy or toxicity in a patient-specific way. In certain cancers such as lung cancer, patients should be tested for mutations in up to seven genes [1]. Anti-cancer drugs whose efficacy relies on the presence of mutations independent of organ or tissue of origin have been approved by the FDA, including Pembrolizumab (an anti-PD1 antibody) in MicroSatellite Instability positive (MSI+) tumors [2] and in tumors with high Tumor Mutation Burden (TMB) [3], as well as NTRK inhibitors in TRK mutated tumors [4]. These developments collectively argue that every cancer patient should now receive comprehensive genomic testing to tailor their therapy to the genetic makeup of their tumors.

Novel tools such as polygenic risk scores that combine multiple genetic variants are demonstrating promise in being able to predict risk of developing a variety of conditions [5]. Such tools can already identify patients with high risk of coronary heart disease who may benefit the most from prophylactic statin treatment [6] or can help provide more precise diagnosis for diabetes [7]. Whole-exome sequencing can be used to diagnose previously undiagnosable diseases with remarkable accuracy [8]. In the pediatric setting where diagnostic speed is critical, it is now possible to sequence a genome and get a diagnosis in <24 h [9].
We believe that this is only the beginning. Several trends suggest that precision medicine is about to become more predictive. Indeed, precision medicine research is booming, fueled by our collective ability to collect data from thousands, even millions of individuals, analyze differences between individuals, then connect these differences with occurrence of disease (diagnosis), evolution of disease (prognosis) and response to treatment. Large cohorts are being assembled, such as the UK Biobank [10], the Precision Medicine Initiative/All of Us cohort [11], the One Million Veteran program [12], and the Estonian Genome Project [13]. Older cohorts such as the Nurses’ Health Study [14], or the Women’s Health Initiative [15] are being augmented with molecular profiling and other measurements and continue to yield high quality precision medicine research findings [16]. These cohorts provide opportunities for creating predictive analytical models that can predict treatment outcome, disease trajectories or improve diagnosis and are more accurate and more replicable than ever. These models may include molecular measurements together with clinical factors. Indeed, growing research suggests that at least for some diseases, genetics adds predictive power over classical clinical factors [17].

Of course, predictive models do not necessarily need to include molecular markers to be useful. Improved ability to use data from the medical record as phenotype (digital phenotyping) has fueled the development of predictive scores that can predict patient trajectories ahead of time. For example, the Veteran Health Administration (VHA) has developed predictive scores called Care Assessment Needs (CAN) scores that accurately predict risk of hospitalization and are used as part of routine clinical care [18]. Environmental, behavioral and socio-economic factors may soon be integrated into these scores [19]. One barrier to broader adoption of such predictive models is that different health systems use different standards for recording medical data. However, efforts towards standardization are ongoing and have led to models that can predict medical events such in-hospital mortality with high accuracy across multiple centers [20]. The large amount of medical imaging data generated during clinical visits is being increasingly used to produce predictive models that may one day be used routinely for diagnosis or treatment response prediction. For example, it is possible to predict malignant lesions from skin pictures with accuracy that rivals trained dermatologists [21]. An artificial intelligence (AI) model can predict human embryo quality during in vitro fertilization with very high accuracy [22]. It is also possible to teach an AI program to read digitized histopathology images and identify tumor subtypes [23] and detect the presence of specific mutations [24]. Such achievements are largely due to the development and broad availability of deep neural networks, which can be pre-trained on non-medical images and do not require prohibitively large number of images to re-train.

When training data for predictive models is not available in high enough abundance, more data can be generated. Improvement in patient derived model technology means that patient-specific organs or tumors can be recreated ex vivo and tested for response to a large number of drugs and investigational compounds. This allows for collection of thousands of data points per patient, a feat that would not be achievable by treating patients directly [25,26]. There are limits to how reliable such models can be, but when feasible, the combination of molecular characterization of patient profiles together with more response data for many patients can help generate complex predictive models of response to therapy. These models can be further tested in vivo using patient derived mouse xenograft models and eventually in patients.

Ultimately these developments will lead to an improved precision medicine that is more predictive and will benefit an ever-growing number of patients.

Competing Interests

Dr Elemento is co-founder and holds equity in Volastra Therapeutics and OneThree Biotech, two companies that use precision medicine and artificial intelligence technologies licensed from Weill Cornell. He is also scientific advisor and equity holder in Owkin and Freenome.

Abbreviations

AI, artificial intelligence; TMB, Tumor Mutation Burden; VHA, Veteran Health Administration.

References
