The focus of this year’s World Health Organisation (WHO) world health day on April 7th was major depression. The prominence given to depression reflected recent global statistics. Depression has now become the number one cause of disability globally— in both developed and developing nations. The burden of disease from depression has accelerated, outpacing earlier projections that it would become the lead cause of disability globally by 2030. This is cause for alarm at a population health level. Precision medicine offers hope, and antidepressant pharmacogenetics appears at a ‘tipping point’ of clinical wide adoption upon adequate replicated peer reviewed evidence on clinical and health economic utility.

The economic burden of depression is immense. Major depression is estimated to cost US$210 Billion dollars per year in the United States alone. The cost globally is currently estimated at US$1 Trillion dollars per year, with strong (up to four-fold) nett societal health economic benefits from improved depression management. The drivers of this immense economic burden are manyfold.
Depressed populations are less productive populations. Depression is both common and highly role impairing among adults. It impacts sufferers during their prime years of economic productivity. When it strikes during adolescence and early adulthood, it impedes skills acquisition - necessary for high value careers. Furthermore, depression reduces outcomes in a variety of general medical conditions - ambivalent depressed patients more poorly engaging with their general healthcare. These many direct and indirect ‘tentacles’ of depression underpin the staggering economic metrics of its burden. Governments - in both the developed and developing world - are ramping up attention and resources to better tackle depression. De-stigmatisation campaigns are likely to see a wave of help seeking in coming years. But this present as delivery dilemma for governments, health systems, and payors. Affordable, accessible, scalable, effective ways to tackle depression an urgent global health priority.

Screening for and diagnosis of depression remains at the clinical syndrome level, dependent upon patient disclosure of symptoms. Diagnostic biomarkers - both genetic and neuroimaging have - to date - failed to yield adequate sensitivity or specificity for wide clinical application. Furthermore, in Asian and other countries with higher levels of stigma, patients often present obliquely - with somatic complaints - so called ‘neurasthenia’ - further challenging diagnosis. But as Asian governments see rising rates of depression and the impacts on population productivity, de-stigmatisation campaigns will likely expand. Indeed the Prime Minister of India highlighted seeking help for depression in a recent national address.

Higher brain function remains poorly understood. Lack of adequate animal models and the possibility of non-linear (less mathematically predictable) dynamics in complex neurochemical systems has limited pathophysiological insights into
mood systems. The full mechanism of action of antidepressants remains hotly debated. This further help explain poor progress on diagnostic biomarkers. But treatment biomarkers to guide optimal therapy have started to gain traction - particularly pharmacokinetic pharmacogenetic ones. However, understanding of the genetic barriers to help guide optimal antidepressant dosing are only just emerging. These pharmacokinetic barriers are more complex than hepatic metaboliser status alone – the brain also protected by the formidable blood-brain-barrier – whose complex pharmacogenetics is only just starting to come to light.

For more impairing cases of depression (major depression), antidepressant medications are indicated. Lifestyle and ‘think-style’ interventions are often best for less impairing mild cases of depression. But when prescribers do decide to prescribe, they are faced with many medication options and an awareness that a possibly drawn out prescribing odyssey lays ahead till effective pharmacotherapy is found. There are over twenty antidepressants in common use, and inter-individual variability in response (both efficacy and tolerability) is high. It takes around a month to gauge the
clinical efficacy of an antidepressant - due to the slow metabotropic impacts on fronto-limbic brain circuits putatively involved in their mode of action. Optimal clinical dose range can vary from half a tablet to three tablets for most antidepressants. For many patients, several months of heuristic dosing arises, some patients disengaging from care demoralised by the process – dosing key to both efficacy and tolerability. As the renaissance physician (and father of toxicology) Paracelsus famously said - “The dosage makes it either a poison or a remedy.”

Antidepressant pharmacogenetics now offers empirically validated hope to help better guide physicians in selecting optimal antidepressant dosages for their patients. Multiple randomized controlled trials have been conducted 5–7, and the first sensitivity and specificity data has emerged 8. This extends the evidence base from many earlier association studies on hepatic metaboliser status and antidepressant response 9. But further independent replication of studies will be needed before prescribing guidelines green light antidepressant pharmacogenetics for routine use in prescribing 10,11.

Suicide remains the most common cause of death in people aged 15-45 in Australia 12 - a pattern reflected in many developed counties. Worryingly, associated with rapid urbanisation in Asia - and loss of the putative mental health protective effects of village communities - a similar pattern is emerging. But specialised mental health care is either scarce or nonexistent in Asia, and stigma remains high 13. Affordable, implementable, scalable technologies to tackle the accelerating burden of disease from depression are urgently needed, and are being actively sought out by healthcare systems globally.

As the field of antidepressant pharmacogenetics has progressed, more peer reviewed studies of clinical utility and health economic value have emerged, with more empirical data in the pipeline 14. These early data are helping demonstrate improved treatment outcomes with pharmacogenetic guided antidepressant prescribing compared to traditional heuristic prescribing. For busy family physicians, sooner effectively treating depression has a commercial value proposition - higher patient throughput helps the bottom line. Patients with depression often have time consuming care needs – stretching busy physicians 15. For sufferers wary of stigma, effective depression care at the family physician level is also likely to enhance help-seeking. Additionally, potential to avoid the need for costly specialist care is another opportunity. Antidepressant pharmacogenetics is a technology well placed to help facilitate reduced burden of disease from major depression.
In some Western countries around 9% of the entire adult population already take antidepressants. Among military veterans the rate is much higher. Recently Veteran’s Affairs in the USA conducted a detailed review of antidepressant pharmacogenetics such as their level of interest in the field. The Trump administration has declared intent to reduce potential over regulation of health technology, and plans to enhance funding for veterans’ mental healthcare. These public health and political circumstances places antidepressant pharmacogenetics in an opportune position in the United States. The FDA has the difficult but important task of ensuring clinical pharmacogenetic products have sufficient evidence to back claims in order to prevent ‘genomic-snake-oil’ yet also have a social responsibility to ensure evidentiary thresholds and regulatory requirements do not thwart genuine innovation reaching market. Prevention of direct to consumer testing of pharmacogenetics is likely to continue due to risk of patients unilaterally making medication decisions. But there has recently been a relaxation of direct to consumer diagnostic genetic testing - the US firm 23&me recently re-granted approval to offer a suite of direct to consumer disease susceptibility diagnostic genetic tests. This may reflect the altered regulator tone under the Trump administration. More active promotion of such products is likely - driven by (and driving) greater patient awareness of the technology. Indeed, patient empowerment and shared decision making is the new norm in the post-paternalistic era of medicine.

With the US$40 million dollar acquisition of Assurex Health LLC by Myriad Genetic Inc. last August, mental health pharmacogenetics has exploded onto the precision medicine business radar. Their primary pharmacogenetic report is reportedly selling $7,000 units a quarter and growing. It appears beyond oncology and obstetrics, mental health may prove one of the biggest – if not the biggest - real world application of precision medicine.

As in other areas of precision medicine, physician adoption has been slower than hoped to date. This is a multi-factorial phenomenon. In part it’s due to mixed and limited evidence base of clinical utility. But in part it is driven by poor genetic literacy, lack of awareness of up to date evidence, and limited reimbursement coverage for such tests. A sense of loss of ‘control’ by physicians may also be a dynamic in play, but pharmacogenetic tools stand to enhanced shared decision making, bolster patient engagement, enhance compliance to medication, and improve treatment outcomes.

As stigma of depression reduces globally and help seeking accelerates, antidepressant pharmacogenetics is one of the few technologies that promises both better outcomes and reduced total cost of care. The Nobel laureate Neils Bohr famously said “Prediction is very difficult, especially about the future.” Despite this wisdom, I’m willing to bet that antidepressant pharmacogenetics will move from early adopter to early majority phase over the next few years. This represents an immense and historic opportunity to help humanity and generate enormous value in a ‘blue ocean’ market segment. One can only hope that precision medicine does prove to be an effective, affordable, and scalable weapon in the fight against the global burden of depression.

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References