nature medicine

Risk-takers wanted

Treating costly conditions such as Alzheimer's disease may soon collapse healthcare systems around the world, yet companies hesitate to invest in the long, large clinical trials required to discover disease-modifying therapies. New incentives are necessary to turn this tide.

Although there is some disagreement about the right therapeutic target to combat Alzhemer's disease—whether it's β-amyloid, tau phosphorylation or something else—there is overwhelming agreement about how to address many of the other problems that plague this field.

If you were to conduct a poll of Alzheimer's researchers, virtually all would agree that current clinical testing of potential new therapies starts too late, after the brain is severely damaged by the disease. They would also agree that early diagnosis and biomarkers predictive of clinical progression are crucial for combating the disease.

Incorporating these views into clinical-trial design would certainly result in better trials, but such trials would also be very large and very long. Longitudinal studies are beginning to identify people at risk to develop Alzheimer's disease: subjects with subtle cognitive or biochemical changes who, years later, will go on to develop the pathology. But validating these markers in a clinical trial will require the trial to start as early as a decade before the onset of the disease, when the presumptive biomarkers start to appear and before brain damage has advanced too far. More importantly, as biomarkers only help identify people at risk, a fraction of whom ultimately won't develop Alzheimer's, the trial would have to include thousands of patients to allow for these 'false positives' and still pick up a statistically significant therapeutic signal. Such a trial would be prohibitively expensive.

Even though there is widespread agreement that these 'marathon' trials are necessary, companies understandably have very little appetite to embark on them. Owing to the economic landscape plus a long string of frustrating failures, the pharmaceutical industry is increasingly risk averse and unwilling to make the massive investment necessary to answer the siren song of a potential blockbuster drug. Meanwhile, governments around the world continue to watch as the number of people with dementia steadily increases while their resources to meet the needs of this patient population do not.

If a key limitation to conducting marathon trials is financial, then those who foot the healthcare bill and have a keen interest in a new therapy—ultimately governments—should find ways to incentivize companies to jump to the fore. They could get the sirens to sing louder by, for instance, offering tax breaks, subsidizing trial costs or granting patent extensions.

Not every Alzheimer's researcher would agree with providing help of this sort to an industry that has often been perceived as failing to act in the best interests of patients, but support of this nature should not be construed as a blank check. Only those trials likely to provide data that will be useful in the design of future trials should benefit from the incentives. A properly designed trial should incorporate a comprehensive panel of biochemical and imaging biomarkers monitored in parallel with the efficacy of the experimental drug. Combined data on efficacy and biomarker changes will ideally define surrogate markers of efficacy that could help establish early on whether a drug is likely to work, enabling prompt decisions on whether to complete a trial or even on whether to grant early approval to particularly promising drugs.

Companies interested in potential incentives would have to work closely with regulators and other stakeholders to optimize trial design, and only those trials that include a comprehensive biomarker-discovery effort would qualify to receive these incentives. Once pioneering therapies are approved and biomarkers are validated, there would be no need for further marathon trials and, importantly, for further incentives. This would provide a convenient mechanism to prevent the unnecessary growth of a support program that is bound to be expensive in its own right.

Tax cuts and subsidies may not be particularly popular ideas in the current financial climate, but the path of least resistance—clinical trials that start late in the disease process—is unlikely to provide the type of breakthrough that will lower treatment costs. We may be weary of the sirens' song, but we nevertheless carry on sailing toward their rock.