Overcoming barriers to early disease intervention

To the Editor — The editorial in your March 2019 issue1 highlights medicine’s current emphasis on treatment when clinical signs and symptoms of disease are manifested — often at a late stage when curative intervention is impossible and disease reversal is improbable. To date, efforts at early preventive medicine have centered on primary prevention and secondary prevention: the former aims to avoid the onset of disease by both promoting healthy habits and providing preventive clinical services, such as immunization and vaccination, to a broad population; the latter aims to identify individuals at high risk of developing disease and intervene with preventive solutions at an early or asymptomatic stage (Fig. 1). Although immunization and vaccination at the population level have proven powerful approaches for promoting public health, few examples yet exist for secondary prevention in at-risk but ostensibly healthy individuals. Here we describe why secondary prevention has proven so difficult, present some cases for how it could be better implemented, and put forward a rationale for therapeutic drug makers to develop and healthcare systems to adopt (Fig. 2).

Although secondary prevention has been a longstanding healthcare imperative, in many cases, trials using this approach have not improved health outcomes2–4. One reason why these have failed is because the interventions often came too late in the disease process. For instance, even though a randomized trial of the small-molecule β-secretase 1 inhibitor verubecestat was targeted to prodromal Alzheimer’s disease patients at high risk for progression, it failed to meet its endpoints, likely because of mistimed (that is, late) intervention. In this trial, the participants already had cognitive symptoms of mild-to-moderate dementia due to the presence of pathological signs of elevated β-amyloid deposits in their brains; thus, the intervention was probably neither sufficiently effective nor early enough in the disease process to have a chance of therapeutic success. Notably, a worse clinical outcome was observed in the verubecestat group than in the placebo group.

As a general rule, as diseases advance progressively over time, the combined action of known and unknown causal factors damage the integrity of critical biological networks motifs (redundant feedback and feed-forward loops5). Gradually, this disrupts the natural flow of essential cell signaling and leads to a loss of biological function, which ultimately manifests itself in overt disease phenotypes and symptoms. Over time, comorbidities and inefficient polypharmacy treatments take over, and organ systems of the human body undergo irreversible, progressive destruction of biological network motifs. Thus, patients lose their physiologic reserve and succumb to underlying conditions, without the ability to restore health. From a physiological standpoint, for individuals at a high risk of developing disease, it makes sense to act at a point sufficiently early in disease processes when biological network motifs still retain sufficient integrity and function to respond to interventions and prevent further decline — or even reverse it.

To achieve this goal, three key questions must be answered: first, how to identify those ostensibly healthy individuals at high risk of developing disease before they display clinical signs and symptoms; second, how to assess the therapeutic window of intervention in the trajectory from health to disease where an intervention is most likely to prevent progression to symptoms; and third, how to assess whether a particular individual is at a stage in disease progression that lies within the therapeutic window.

Of course, with monogenic diseases, the presence of highly penetrant disease alleles provides a reliable mean of identifying individuals at high risk of developing symptoms. A good example is spinal muscular atrophy (SMA), an autosomal recessive neurodegenerative disease characterized by low levels of the survival motor neuron (SMN) protein due to defective biallelic mutations in the survival motor neuron 1 (SMN1) gene, which causes a loss of motor neurons, progressive muscle weakness, and atrophy of skeletal muscles, ultimately leading to death. There are several types of SMA: the most severe (type 1, Werdnig–Hoffman disease) leads to death by two years of age, with the worst-case scenario involving death in the first month of life (sometimes termed “SMA type 0”). Although the underlying pathology of SMA is not fully understood, deficits in SMN levels and signaling via interacting biological network motifs severely and irreversibly affect neuronal survival5–7.

Preclinical studies from different groups have revealed the existence of a very short intervention window to increase SMN to optimum levels by replacing the defective SMN1 gene with a functional copy6,8. In those preclinical studies, mouse pups with a deletion in SMN1 (SMNΔ7) treated on postnatal day 1 with a single intravenous injection of 5 × 10¹¹ self-complementary adeno-associated viral vector serotype 9 (scAAV9) particles carrying functional SMN1 achieved complete rescue of motor function, muscle physiology, and lifespan. Treated mice had an average lifespan of more than 400 days, as compared with ~16 days in the untreated animals. Notably, those preclinical studies also showed that the earlier the intravenous injections of the scAAV9-based gene therapy, the greater the therapeutic effect in postnatal mice. As such, this approach has its maximal effect on postnatal day 1, an effect that decreased rapidly with advancing age: injections on day 5 had only a partial effect while injections on postnatal day 10 had no effect.

The above studies indicate that interventions designed to increase SMN expression to optimal levels require very early delivery of a functional copy of SMN1 before manifestation of observable signs and symptoms. This observation was confirmed by in vivo pharmacological studies of the gene therapy Zolgensma (onasemnogene abeparvovec-xioi) conducted in SMNΔ7 mice9. Such data provide a strong rationale for timely disease intervention programs in at-risk newborns, including considering surrogate endpoints other than clinical symptoms consistent with SMA type 1.

According to the clinical trial study description of Zolgensma, all patients enrolled in the phase 3 trial experienced onset of clinical symptoms consistent with type 1 SMA10; however, Zolgensma worked in only about half of the patients treated. A phase 1 trial showed that efficacy in more patients could be increased at a higher dose, but this increased the likelihood of serious side effects from the treatment, such as severe liver injury, myocardial degeneration and atrial thrombosis. These results suggest a role for prenatal screening for SMN1 mutations, with the possibility of treatment shortly after birth for those who are identified as high risk.

Clearly, monogenic diseases are rare in the population, and it should be emphasized that many are still neither simple to comprehend at the genetic level nor easy to predict concerning the timeline for manifestation of clinical symptoms. However, biomedical advances are leading to a better understanding of the intrinsic etiology of some monogenic ailments,
Identifying culprit mutations that could be amenable to timely intervention windows with the right solutions — before clinical manifestation of observable signs and symptoms.

When it comes to the etiology of complex diseases, such as adult-onset neurodegenerative diseases, cancers and metabolic disorders, the situation is much more challenging, as the cause(s) of most of these diseases remains poorly understood. Large portions of the genetic risk arise from mutations in more than one gene, with complex epistatic interactions of gene products. The challenge is compounded by a convergence of intrinsic, extrinsic (lifestyle, dietary, environmental and holobiont) and idiopathic factors. Even so, for certain complex chronic diseases, there may be opportunities for an early therapeutic window of intervention, even with the current state of knowledge.

For instance, in type 1 diabetes mellitus (T1D), it is now possible to profile genetic risk at birth (for example, genes include interferon-induced helicase C domain-containing protein 1 (IFIH1), sialic acid acetylerase (SIAE) and the interferon regulatory factor 7 (IRF7)-driven inflammatory network (IDIN)) and track biomarkers (for example, glutamic acid decarboxylase (GAD) and protein tyrosine phosphatase (ICA512) autoantibodies against pancreatic beta cells) in childhood (5–7 years) to identify suitable intervention windows before both late asymptomatic disease and when observable symptoms are manifested typically around puberty. Although an effective, commercially available T1D early intervention therapy is still missing, great strides are being made. On 5 August 2019, the US Food and Drug Administration granted Breakthrough Therapy designation to teplizumab, an Fc receptor–non-binding anti-CD3 IgG2 monoclonal antibody under development to act as a T1D prevention therapy. The treatment aims to alter the physiology of the T cells that target pancreatic islet beta cells. During early 2019, using surrogate endpoints (stage 2 T1D), results from phase 2 clinical trials with patients at risk of developing T1D showed that 57% of teplizumab-treated patients did not develop the condition, as compared with 28% of placebo–administered patients. To increase the effectiveness of an alternative preventive therapy for T1D, it might be necessary to optimize the intervention timing using stage 1 T1D surrogate endpoints, before autoimmunity is triggered.

In the case of cancer, successful early intervention strategies have also been shown. For example, high-risk smoldering multiple myeloma (SMM) has been used as surrogate endpoint in progression to multiple myeloma, before organ-level network motif damage and symptoms occur. Yet current clinical dogma recommends a “wait and watch” strategy for SMM patients, in which medical interventions should begin only upon multiple myeloma symptom development.

In 2015, a single-arm pilot study at the US National Cancer Institute treated 12 patients with high-risk asymptomatic SMM with a combination regime including the proteasome inhibitor carfilzomib and the immunomodulatory drugs lenalidomide and dexamethasone, resulting in 12 of 12 (100%) experiencing a near-complete response and 11 of 12 (92%) minimal residual disease–negative rate. These clinical outcomes build off preclinical evidence showing that the proteasome inhibitors and immunomodulatory drugs have synergistic activity mediated by enhanced proteasome targeting, caspase activation, nuclear factor kappa B (NF-kB) inhibitory activity, and downregulation of CRBN/IRF4/MYC signaling and MCL1.

Recently, a meta-analysis, including studies from January 1990 to March 2019, investigated the optimal timing of treatment for patients with SMM at high-risk, examining differences in progression, mortality, response and safety between early treatment and deferred treatment of SMM. Findings suggest that early treatment could decrease progression and mortality in patients at high risk, with a tolerable safety profile.

The above cases illustrate the dependence of the early intervention paradigm on our ability to diagnose disease trajectory with a high degree of certainty on the basis of presymptomatic predictive biomarkers. This is important as we want to neither overtreat those who are not progressing toward symptomatic disease (false positives) nor miss people who will become symptomatic (false negatives) and lose the opportunity to pre-empt disease. Depending on the specific nature of the intervention approaches, the risks involved, and the window of time in which one can act, we as a society may be willing to accept varying degrees of either false positives or false negatives. For instance, an intervention approach with little risk (such as a vaccine) but with a limited window of effectiveness could tolerate a high degree of false positives, but one would want to minimize the number of false negatives.

For different diseases, we may be able to assess what individuals are at high risk for developing future disease; however,
assembling where they are in disease trajectory (‘disease staging’) and whether they are in the therapeutic window for intervention requires information from many individuals’ disease-specific trajectories. Identifying individuals at high risk requires identifying ‘at-risk markers’, and staging disease in those individuals requires identifying disease-specific ‘tracking markers’ to monitor the earliest presymptomatic signs of disease progression. At-risk markers may be influenced by a combination of causal genetic (for example, single highly penetrant alleles or polygenic risk scores), lifestyle, environmental and holobiont factors. Tracking markers may involve pathophysiological phenotypes indicating unhealthy biochemical, metabolic and physical functions, as well as abnormal emotional, cognitive and behavioral states.

Defining a therapeutic window for intervention will require a subgroup analysis for each medical condition. High-risk individuals will need to be stratified, segmented and clustered on the basis of the interplay between specific tracking markers and environmental stressors that may influence disease progression toward symptomatic states. Thus, for each medical condition, there may be several windows for interventions, depending on risk and disease progression profiles of different subgroups of patients.

As mentioned before, disease staging involves identifying tracking markers. Yet these markers may be classified as necessary, sufficient or contributing causes to specific medical conditions. On the one hand, if tracking marker x is a necessary cause of disease y, then the presence of y necessarily implies the prior occurrence of x. However, the presence of x does not imply that y will occur. On the other hand, if tracking marker x is a sufficient cause of disease y, then the presence of x necessarily implies the subsequent occurrence of y, but another cause z may alternatively cause y. Thus, the presence of y does not imply the prior occurrence of x. As such, unless validated, the relationship between a tracking marker and direct clinical benefit may not be causal.

The above information exemplifies the difficulty of dealing with complex systems, such as human biology. Therefore, choosing a favorable timeframe in which a therapeutic intervention should be performed to prevent progression of pathologic processes that lead to symptomatic disease must be supported by strong mechanistic and epidemiologic rationale in defined subgroups.

Perhaps the biggest challenge in the implementation of broader and more effective early disease intervention is the lack of appropriate and sufficient data for this type of approach. Identification of diseases that are best suited to an early intervention approach, determination of appropriate diagnostic and therapeutic windows for those disease, and selection of optimal tracking markers will be dependent on large-scale multidimensional datasets from both normal and disease states. This will allow a more complete understanding of the complex nature of interactions between such elements as the genome, proteome, phenome, microbiome and mobilome, along with environmental and societal factors.

Fortunately, several large-scale initiatives across the world are underway with the aim of collecting such data from individuals to help improve our understanding of health and disease susceptibility. For instance, the UK Biobank has enrolled over 500,000 ostensibly healthy people for a combination of genome sequencing and measurements of behavior, social life, mental state, lifestyle, diet and physical health. In the United States, the National Institutes of Health’s All of Us Research Program aims to gather biological, lifestyle and environmental measurements on a million or more people in the United States. In China, a joint venture between the Chinese Academy of Medical Sciences and the University of Oxford is the China Kadoorie Biobank (CKB). The CKB will investigate the main genetic and environmental causes of common chronic diseases in more than 515,000 individuals in the Chinese
population. These efforts are important because they diverge from the traditional focus on disease care in biomedical research. Moreover, these initiatives raise hope that we can begin to collect the data necessary to carry out in-depth analyses on different subpopulations of individuals with the goal of identifying the best way to combat disease at a meaningful early stage. Figure 2 shows a hypothetical illustrative example of the early disease intervention paradigm, showing stage-specific goals, potential data required, possible solutions to challenges, and the deliverables that would be made available to the healthcare ecosystem.

Once such data are available and analyzed, we stress that selective approaches to screening are still necessary to ensure cost-effective solutions to early intervention. To compare to a current example in medicine, colonoscopy is a cost-effective form of secondary prevention; however, computed tomography to screen for a wide range of intra-abdominal cancers is not. Incidentalomas can result in substantial anxiety for patients, despite unclear significance of the unanticipated findings, and may lead to expensive and unnecessary additional diagnostic testing. Accordingly, screening and early detection are of limited value (and may even be detrimental to the patient) if abnormalities cannot be promptly and effectively corrected.

For the early-intervention paradigm to be adopted more widely, it must overcome an existing culture in which the medical establishment emphasizes disease treatment rather than health and prevention. Time-tested endpoints measuring observable symptomatic outcomes will continue to be an important part of medical practice focused on disease care. However, there must be a shift away from the present paradigm, in which preventive approaches have been unable to specify effective time-sensitive, disease-specific intervention windows for individuals. The failure to appreciate this has dogged past prevention trials, with several ‘early detection and intervention’ approaches failing to define the right therapeutic window to prevent, halt or inhibit progression of disease.

In particular, the early intervention model must show clear economic advantages over the current model. The starting point is for healthcare systems and payers to become convinced that early intervention offers savings and a better return on investment than treatments for end-stage disease. Drug makers could be incentivized to develop early interventions by the prospects of future favorable engagement with regulators and payers to realize a return on investment. In some cases, early intervention treatments could be chronic, given over one’s lifespan to maintain health; in other cases, they may be single-shot therapies given only once in a lifetime to permanently prevent or cure disease. Regulators will need to consider how to approve effective early-intervention approaches on the basis of validated surrogate endpoints when success means that nothing happens (that is, there are no symptoms to reverse). When there are no symptoms to reverse, regulators must learn to be comfortable with the ongoing absence of disease as a marker of success in a patient who never demonstrated signs or symptoms of the disease.

In turn, early intervention could provide cost savings for payers over a lifetime of coverage in comparison with end-stage disease therapy, providing access to therapies with reimbursements set at specific price points aligned with quality-adjusted life years gained by the individual after treatment. Thus, successful prevention early in life could prove to be cost-effective over the long term; it could protect not only at-risk asymptomatic individuals from moving past triggers of symptomatic disease, but also health systems from extensive and expensive medical evaluations, not to mention ineffective and costly treatments for end-stage disease. However, such collaboration between drug manufacturers and payers would require cost-sharing agreements across payers who, in healthcare economies like that of the United States, are subject to shifting risk pools as subscribers move across payers based on employment or health enrollment status.

Implementing effective early-intervention approaches will be difficult if patients and consumers continue playing the role of passive recipients of disease care. In many cases, it is very difficult to induce behavior change in ill people. But it is even more challenging to induce behavior change in seemingly ‘well’ people — particularly sustained behavior change. Therefore, effective early intervention windows will likely have to be accomplished through a holistic approach that engenders true patient and social engagement to achieve its maximum potential. Intriguingly, research evidence from social physics has shown that, for certain medical conditions, influencing a particular health behavior depends on exposure to peers with whom we have relatively little intimate interaction, rather than family and friends. The study suggests that focusing on social network incentives rather than a traditional individual-centric approach is more effective at altering the flow of ideas and behavior by creating positive social pressure, increasing the amount of interactions around specific target ideas, and thus increasing the likelihood that people will incorporate those ideas into their behavior.

Taking all the above into consideration, identifying and exploiting effective windows for early disease intervention may require an initial focus on highly penetrant disease alleles. Thus, besides SMA, other rare Mendelian diseases such as phenylketonuria and tyrosinemia could be addressed.

Regarding complex chronic diseases, besides diabetes, some neurodegenerative disorders might be best suited for effective early preventive approaches. One of the most challenging areas of biomedical research is Alzheimer’s disease. There are as yet no effective therapies that prevent, stop or reverse its progression. Instead, there is a growing graveyard of last-resort symptomatic drugs that have failed.

Ideally, an effective early intervention for Alzheimer’s disease might require monitoring a narrower intervention window, before cognitive symptoms of mild-to-moderate dementia appear, but with early signs of pathology on brain imaging or in cerebrospinal fluid tracking markers. It is now generally accepted that pathophysiological biomarkers such as low β-amyloid 42 (Aβ42) in cerebrospinal fluid and scarce cerebral amyloid deposits precede clinical symptoms. Preclinical diagnosis would require targeted population screening, which is currently only recommended for research purposes. Nevertheless, the ability to use genetic at-risk markers to define high-risk individuals and to use brain imaging and biochemical tracking biomarkers to monitor and stratify these individuals may ultimately lead to effective early intervention in Alzheimer’s disease with the right solutions.

Several scientific, regulatory, cultural and commercial challenges still exist to overcome barriers to broad early disease intervention, precision medicine, and personalized health care. In an increasingly cost-conscious healthcare ecosystem, engaging diverse stakeholders to support a focus on health care in ostensibly ‘well’ people is certainly not business as usual.

Nonetheless, these challenges can and must be addressed. The shift from volume to value has created opportunities for fundamentally new health economics and next-generation healthcare strategies. By seizing effective windows for early disease intervention, we emphasize special attention to health rather than disease, improved outcomes instead of narrowed symptomatic solutions, and care coordination as opposed to care duplication. Over time, stakeholders will realize that the true medical and financial value of personalized medicine...
To the Editor — The development of rapid and reliable molecular diagnostic tests for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is paramount for controlling the COVID-19 pandemic. A similar scenario was faced in the Ebola virus outbreak in West Africa, in which rapid, reliable tests were key to controlling the outbreak. However, in the rush to scale up testing availability, the importance of standardization, though critical, is often overlooked by laboratories when setting up assays. As an example, different sensitivities of real-time RT-PCR (RT-PCR) kits can have considerable clinical impact because different tests might yield undetectable results at different time points, potentially influencing how long patients were kept in isolation. The authors recommended that results be reported in international units (IU) per milliliter using an international quantification standard. At the time of the outbreak, it was recognized that the use of reference standards would help provide reliable and robust assays, and current recommendations are to use a World Health Organization (WHO) International Standard (IS) in assays as and when it becomes available. Moreover, the WHO produces Target Product Profiles that include the need to include standards in assays.

The WHO and its collaborating centers for standards, the Paul Ehrlich Institute (Germany), the US Food and Drug Administration’s (FDA) Center for Biologics Evaluation and Research (CBER) and the UK’s National Institute for Biological Standards and Control (NIBSC), have an ongoing program to develop an IS to harmonize the measurement of pathogens in diagnostic assays. For emerging diseases that require biocontainment (Biosafety Levels 3 and 4), packaging pathogen-specific sequences in lentiviral vectors proved to be very effective in harmonizing the measurement of ebolavirus by nucleic acid test (NAT). As has been consistently shown in collaborative studies performed to establish an IS, the varying performance of individual laboratories’ assays against an in-house standard typically leads to a wide variety of results for the same sample (Fig. 1a). It is possible that this could result in different clinical decisions for patients, depending on which lab their sample was tested in. However, calibration against an IS effectively eliminates this variability to a large degree (Fig. 1b). This has important implications not just for individual patients, but also for the reproducibility and reliability of data in clinical trials, such as those to establish the immunogenicity of novel vaccines.

Urgent work is ongoing, in collaboration with the WHO, to develop interim reference materials that will assist in harmonizing NAT-based diagnostics for SARS-CoV-2. Although these materials will not be available immediately as formal standards, similarly produced full-genome reagents are already available from the NIBSC (via covid19_reagents@nibsc.org, catalog number 19/304). The consistent use of standards will help to establish diagnostic assay performance and support the early development of accurate and reliable tests with comparable sensitivity. We strongly encourage the scientific community and diagnostic labs to strive for standardization and employ relevant reference materials as