Preempting Chronic Diseases Before They Start: A New Healthcare Focus to Keep People Healthy

October 2023

Kitalys Institute | UsAgainstAlzheimer's | Flagship Pioneering

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EXECUTIVE SUMMARY

The Kitalys Institute convened a global online event focused on "Opportunities and Challenges for Preempting Chronic Diseases Before They Start." The discussions centered on the need to challenge the traditional healthcare model, emphasizing a shift away from the current sickness-centered approach. Speakers explored how advances in the biological and computational sciences provide enormous opportunities to detect and attack disease before it takes hold, but noted a lack of “secondary prevention” strategies focused on detecting pre-disease in seemingly healthy people to prevent or delay disease progression. For effective preemptive interventions, speakers unanimously stressed the importance of robust biomarkers and intermediate endpoints, as well as regulatory validation, public-private partnerships and data source integration. Acknowledging the financial burden of chronic diseases, speakers advocated for changes in payment and delivery systems, as shifting from treating sickness to preventing it necessitates restructured healthcare financing.

The event concluded with a resounding call to mainstream preemptive health and medicine. Regulatory agencies, industry stakeholders, payers, and research communities were urged to collaborate to develop a roadmap for identifying preemptive biomarkers and endpoints and addressing regulatory and payment policy changes. Both U.K. and U.S. regulators signaled willingness to engage in structured workstreams, highlighting a shared commitment to advance preemptive medicine. The event underscored the transformative potential of preemptive health and medicine on population health and quality of life, as well as the sustainability of healthcare systems.

INTRODUCTION

On September 13, 2023, the Kitalys Institute hosted a global online event examining "Opportunities and Challenges for Preempting Chronic Diseases before They Start." The event, which attracted over 800 global registrants, was moderated by George Vradenburg, **Chairman and Co-Founder of UsAgainstAlzheimer's**, with an introduction to the topic provided by **Lord Ara Darzi, Chairman of the Preemptive Health and Medicine initiative at Flagship Pioneering**. They were joined by an extraordinary panel of speakers, including:

- **Dame June Raine, CEO of the UK's Medicine & Healthcare Products Regulatory Agency (MHRA)**;
- **Dr. Samantha Roberts, CEO of the UK's National Institute for Health & Care Excellence (NICE)**;
- **Dr. Mark McClellan, former Commissioner of the U.S. Food & Drug Administration (FDA) and former Administrator of the U.S. Centers for Medicare & Medicaid Services (CMS);**
- **Mr. David Ricks, Chairman and CEO of Eli Lilly & Company**; and
- **Dr. Hilary Evans, Chief Executive of Alzheimer's Research UK**

This white paper seeks to capture the rich discussion among the esteemed panelists on the promise and challenges of preemptive medicine, and summarize how the community of relevant stakeholders can work together to accelerate the development of preemptive interventions to delay or preempt chronic disease.

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Healthcare or sick care?

Lord Darzi opened with an expansive definition of the opportunity and challenge: "Our shared understanding of what it means to be healthy is predominantly defined as the *absence* of sickness rather than the presence of health. We normally understand ourselves to be sick when we experience the symptoms of a particular disease or condition."

Lord Darzi continued: Sickness is, of course, the arena in which most medicine is practiced – diagnosing, treating, and managing illness, whether episodic or chronic. As a result, our healthcare systems are actually sick care systems. This observation is not meant to denigrate their importance; they are essential to the good functioning of a civilized society. But studies have found that less than 5% of health resources are dedicated to keeping people healthy. It is therefore

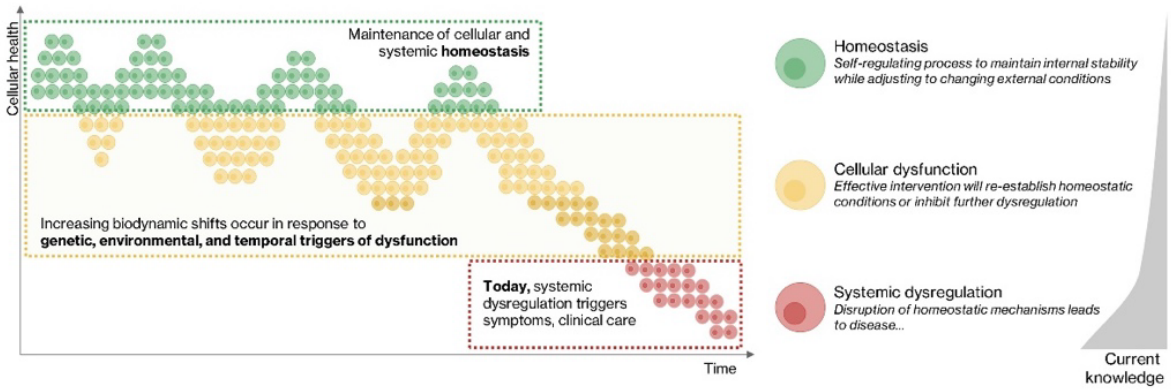
unsurprising that more than two billion people today around the globe are living with one or more chronic diseases.

The continuum between health and sickness

Physicians and scientists have understood for many years that reality is much more complex than a simple dichotomy of sickness and health. “There is, in fact, a continuum between health and sickness and the journey from one state to the other is rarely linear,” Lord Darzi observed, continuing: “If health and sickness were black and white, there is an awful lot of gray in between.”

As explained by Lord Darzi, it is Flagship’s belief that the same applies at the cellular level. In a healthy state, homeostasis is a self-regulating process that maintains internal stability – both cellular and systemic – while adjusting to normal changes in external conditions. Disease is where homeostasis is no longer maintained at either the cellular or systemic level and symptoms manifest. In between, Flagship believes that there are identifiable “biodynamic shifts” that occur in response to genetic, environmental, and temporal triggers of dysfunction. These shifts are detectable and measurable through various biomarkers or diagnostic measurements. This is illustrated below:

We believe that there is a period between health and sickness when individuals begin their trajectory towards disease



Flagship terms this middle phase “pre-disease,” which occurs in *seemingly* healthy people. It commences at the earliest stages of cellular dysfunction and encompasses the earliest stages of asymptomatic disease; in all cases, these individuals are on a trajectory towards a disease state, but have not arrived at it. People living with pre-disease might be termed “pre-patients,” according to identified biomarkers.

"Too late for public health, too early for clinicians"

This approach of detecting disease in seemingly healthy people in an effort to prevent disease progression is generally termed "secondary prevention." In contrast, primary prevention strategies aim to lower the incidence of disease in populations by tackling risky behaviors such as smoking, whereas tertiary prevention aims to limit the severity and impact of disease on people who already have symptomatic disease.

Primary prevention is well served by public health professionals and tertiary prevention is the domain of physicians and other clinicians, particularly through recent developments in accountable care programs. But as Lord Darzi noted: "Secondary prevention has been somewhat an 'orphan child' – too late for public health, too early for clinicians."

There are only a small set of activities – such as screening programs and blood pressure monitoring – that are aimed at detecting subclinical disease. While there are a handful of powerful interventions, secondary prevention remains a much more limited area. For example, the U.S. Preventative Service Task Force has only four recommendations for preventative medication with a high or moderate certainty of benefit.

As Lord Darzi explained, "Too little time, attention and resources are dedicated to examining and exploring the potential of secondary prevention to create value for individuals, health care providers and systems as well as societies and economies."

"Preemption is an action — prevention is an outcome"

Why preemption rather than prevention? "'Prevention' is effectively a promise that disease will never occur – a bar that is so high that it dissuades innovation and imposes impossibly long development cycles for any possible drug discoveries," noted Lord Darzi, continuing: "It is right to be impatient in the here and now."

Even if a particular pre-disease could not be prevented, stopped, or reversed, it is easy to imagine the enormous value that could be created for individuals and communities if the onset of a chronic disease could be delayed even just by five years. As Lord Darzi said, it could mean "Five more years of being able to stay in work. Five more years without pain or disability. Five more years of being well

enough to play with the grandchildren. Just slowing down the onset of symptoms could transform the lives of many people."

"Regulators have a duty to help the preemptive health agenda to flourish"

In her opening remarks, Dame Raine emphasized that "regulators have a role and a duty to enable innovation [and] not to keep patients and the public and payers waiting … Especially now that we have the pipeline coming of really interesting new [molecular] entities around … obesity, dementia, [and] risk modifying drugs." Indeed, she added that "regulators have a duty to help the preemptive health agenda to flourish."

Dame Raine continued: "We have the opportunity of real-world data, large datasets, and let's bring on more international collaboration in this space. Regulators are increasingly more comfortable to base labeling decisions on real-world data … [In the UK] we've got 'Our Future Health,' which is the program that's going to look at disease risk scores in five million people … So five million disease risk scores, what are we going to do with that evidence?"

On the cusp of transformation, biomarkers & intermediate endpoints are critical to unlocking preemptive medicine's potential

All speakers agreed that biomarker development and validation are critical to unlocking the potential of preemptive health and medicine. As MHRA CEO Dame June Raine noted: "Critically important for us is going to be robust data that links this early diagnosis based on, say, biomarker evidence with predictors of benefit at particular points at that stage going from the pre-disease state … balancing it against the product's risk." This was further reinforced by NICE CEO Dr Samantha Roberts, who emphasized: "The risk associated with intermediate endpoints is that we are not going to know whether these interventions affect length and quality of life for sometimes decades … the way that we can significantly mitigate [that risk] is by properly investing in research on intermediate endpoints."

Lilly CEO Mr. Ricks added that robust public-private partnerships will be essential in this area, as the private sector is unlikely to take on the risk of such large studies by itself, and without the buy-in of regulators. He also highlighted some of the challenges around the science and the relationship between the benefit and clinical risk. He explained that his company is working on ways to prevent cardiovascular disease and diabetes by using obesity medicines and to prevent Alzheimer's disease with an anti-amyloid medication: "We are on the cusp of

beginning to address diseases before the clinical symptoms manifest at some scale. The point of origin problem for us is the tractability of the science. We look at targets identified by others and then seek to interfere with biology in a way that can become a widely used product or medicine … If we don't know the targets, we're really not going anywhere in this problem. If we know the targets, having symptoms or not is less important." He added that: "The benefit-risk in that [pre-disease] setting has to be higher than in a treatment setting because the patient is not experiencing symptoms and the probability of conversion to a symptomatic condition is less certain, no matter how good our predictive marker is." He continued: "So you have to have better drugs, they have to be incrementally safer or more effective or both to want to test them in this setting … I don't think our drugs have been good enough to be used as preventatives because we haven't understood very well the structural biology and the way that the medicines are interacting with biology. That's changing."

Alzheimer's UK CEO Dr Hilary Evans described how new biomarkers were the first pillar of the UK's Dementia Mission. She made the case that: "We need larger sample sizes, we need better biomarker stratification, we need better risk identification, and we need the tools to do this." She emphasized the need for a data platform that would pull various sources together and provide insights into who in the population was at risk. This would need to be confirmed with diagnostics.

The timing of benefits was another key point for discussion. Dr. Roberts explained: "I'd love to see us working together with the scientific community, industry, regulators on what are those intermediate endpoints that we can all invest in getting right, but that correlate with length and quality of life." This point was echoed by Mr. Ricks, who noted that "in most of the important diseases to prevent, we actually don't know the time course of the pre-condition. And so, if you pick the wrong point to intervene and it's not a linear relationship between time and the disease, you have a big risk [in terms of successful product development]."

Changes to payment and delivery systems

The rising tide of chronic disease – many the result of modern lifestyles – means health systems are under sustained financial pressure. Indeed, Flagship projects that, if healthcare costs in the U.S. grow at the same pace for the next 30 years as they have for the past 30 years, then healthcare will account for 32% of the U.S. economy by 2050. Improving the efficiency of healthcare services and eliminating

waste will not be a sufficient response to the scale of the challenge. Flagship argues that the only path to sustainability is to improve the health of the population by preempting sickness through innovation.

Dr Mark McClellan, former FDA Commissioner and CMS Administrator, acknowledged that "there are great opportunities for preemptive medicine," while noting that "changes would be needed to payment and delivery systems" in order to realize its full potential. As Mr. Ricks pointed out: "Health systems aren't particularly ready for the volume that may be coming their way. They're built for treating sickness, not preventing sickness."

Dr McClellan described how the sick care paradigm was shifting, using the example of cancer care. Historically, new products would focus on advanced disease where there were no existing treatment options available, meaning the risk-benefit was uncomplicated and the regulatory pathway was clear. However, with the development of liquid biopsy – such as the multi-cancer early detection tests being developed by multiple companies (including Flagship-founded Harbinger Health) – the treatment paradigm is shifting to much earlier-stage detection. This would create new challenges, Dr McClellan noted. But the reality was that "in the U.S. and the UK, the financing paradigm for healthcare is about tertiary prevention and helping people who really need help."

What could change that? The shift towards "Accountable Care" – paying for outcomes rather than specific services – could help healthcare systems to move upstream. Dr McClellan described how the U.S. had seen some examples of a shift to being paid on a "longitudinal" basis, which had resulted in "a lot of innovation and culture change in healthcare … [to] really build community health systems."

Dr McClellan argued the public sector had to rally behind developments in preemptive health and medicine: "Private sector innovation is really important, but it's hard to see it really succeeding at scale without Medicare getting even further behind these early interventions."

The panelists also discussed how payers view preventative interventions generally, which Dr. Roberts noted typically do not save money once a full accounting of costs is assessed (including the costs of reaching and testing broad populations) and the decline in adherence over time dilutes the health and financial savings of preemption is taken into account. There was a consensus that

cost effectiveness, rather than savings in absolute terms, is the proper way for payers and society to assess the value of such interventions.

The panelists also discussed the need to address the individual "demand" side of this health system challenge. Dr McClellan pointed out that getting people to pay "attention to adherence [to preventative regimens] when people have so much else going on in their lives is really hard." Similarly, Dame Raine noted the challenge in effective risk communication with the public: "I don't think we communicate risk very well in accessible ways for patients and the public. We are going to need to take the public with us on this journey. And I'd really like to see this opportunity grasped by regulators to help the public come with us as we move forward with preemptive health."

"Let's mainstream preemptive health and medicine"

At the conclusion of the session, Dame Raine issued a rallying call, saying: "Let's mainstream preemptive medicine, preemptive health, that the science is driving and the science is being done!" For his part, Mr. Ricks emphasized the potentially dramatic impact of a preemptive health and medicine approach in collaboration with UK regulators and payers, stating "I think it's possible we could make the UK the first obesity free country in the world." And Dr McClellan emphasized the importance of disseminating the ideas more widely: "Overall the arc seems to me to be going in the right direction. We're paying attention to the right issues clearly here. Hopefully the findings from this discussion can make it out more widely."

Lord Darzi closed the meeting with an observation and call to action: "Most people overestimate what they can do in one year and underestimate what they can achieve in ten years. With the right investment and regulatory frameworks, it is our belief that preemptive health and medicine could have extraordinary impact over the next decade."

Moving forward

It appears from the discussion that the most critical next steps to advance a preemptive medicine approach is to bring key regulatory and payer agencies, potential industry sponsors, and the relevant research community together to (1) develop a roadmap for the identification/development of the data that will be needed to properly assess preemptive biomarkers and intermediate endpoints; and (2) assess the specific regulatory or payment policy changes that may be

needed to facilitate the development, approval, and adoption of preemptive interventions.

There was affirmative support for this approach from the UK government participants, and – in a separate Kitalys-hosted event with current FDA Commissioner Dr. Robert Califf in May 2023 on the same topic – he, too, signaled willingness for the U.S. agency to engage in a structured workstream with other stakeholders to explore these important issues.