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Healthcare / Biotechnology

THREE PATHS TO LONGEVITY: SCIENCE EXPLORES NEW DRUGS, GENE TESTING AND PRECISION MEDICINE

In the United States there are now 46 million people above the age of 65, with demographers expecting that number to double over the next 40 years. Further, for the first time, about one-fifth of people in Japan are age 70 or older, and the proportion over 65 is 28.1 percent of the population. Meanwhile, in China, 123 million people are over 65 and 240 million are over 60. The aging of the world's population can't be denied. The question that science is pursuing with increasing gusto is, how can this aging population live not only longer but also more comfortably into old age? Medical research appears to be focusing on three categories of answers: new drugs, genetic testing and precision medicine. (*Precision Vaccinations*, 12/12/18; *Nikkei Asian Review*, 9/17/18)

TAKEAWAYS

- Large portions of the world's population – in both developed and developing countries – are aging, and researchers are focused on finding ways to help people live a long and high-quality life.
- Researchers are examining a variety of new drug classes that appear to have a body-wide overall effect to improve well-being.
- Information from genetic sequencing is enabling physicians to create "score cards" on the risk of numerous diseases for individual patients, enabling those patients to seek early intervention and to reduce their risk through regular screening and lifestyle changes.
- Several advanced technologies, such as genomic sequencing and "organs on a chip," enable doctors to treat patients in a more precise way based on their bodies' individual unique qualities rather than what works best for the general population.

IMPLICATIONS

- In the next decade, for the well-heeled, healthcare spending will increase on a variety of novel tools currently under development to fight aging and disease.
- In the near future, more health plans will include genome sequencing and analysis as part of routine ongoing care, especially as patients approach old age, or as a one-time test for infants to carry in their life-long medical records.
- New forms of medicine will accentuate the have/have-not split in our society.

New Drugs to Boost Longevity

In recent years, medical research has uncovered different categories of drugs that appear to have a broad, systemic and universal effect on well-being, such as by enhancing the body's ability to fight infections in general, improving the body's overall metabolism in a way that holds obesity-related conditions at bay, augmenting the body's ability to eliminate infirm cells, which keeps the body feeling "younger" for longer or replacing important bodily chemicals that diminish as we age. Consider:

• A clinical trial involving people aged 65 and over found that giving them two drugs in a category called mTOR inhibitors led them to experience nearly half as many infections over the following year as a control group that received placebos. In numerous studies, the application of mTOR inhibitors has extended the lifespan of every species they've been tested on. (*Guardian*, 7/11/18; *MIT Technology Review*, 7/18)

"Scientists have isolated the gene that makes scientists want to isolate genes."

• Research in recent years has found that a group of seven proteins in the human body known as sirtuins contributes to longevity. A key chemical in human cells called NAD+ activates these sirtuins, but as we age, NAD+ levels naturally drop. A company called Elysium Health has created a daily supplement, Basis, which boosts NAD+ levels (whether it thereby increases longevity has not been evaluated by the FDA). (*Good Housekeeping*, 12/26/18)

• At least three drugs are being researched that appear to mimic the effects of exercise, one by activating a gene that is similarly activated by endurance exercise, one by lowering blood-glucose levels and one by transforming inert white fat into energy-burning brown fat. (*New Yorker*, 10/29/17)

• Senescent cells are cells in the human body that are not completely dead but are too damaged to function properly. Such cells build up in the human body as we age and lead to frailty. In several animal studies, removing these cells reverses signs of aging. A new drug that appears to help clear senescent cells from the human body, dasatinib, was tested on a mere 14 seniors in a first-stage safety trial – but initial results are promising as the test participants were able to walk faster and stand more quickly, and scored better on physical ability tests after taking the drug. (*Telegraph UK*, 1/9/19)

Get a Report Card at Any Age

In addition to the kinds of treatments being explored above that can help anyone deal with aging in general, the realm of genetic testing promises to allow people to get more personal with managing their health. Researchers are working on so-called genetic report cards, or "polygenic risk scores," that aim to assign patients risk numbers for various diseases and traits based on analysis of their DNA. For instance, score cards being developed by the Broad Institute in Cambridge (MA) can provide patients with their personalized risk profiles regarding five serious common ailments: heart disease, breast cancer, type-2 diabetes, inflammatory bowel disease and atrial fibrillation.

These tests and scores are emerging from analysis of large pools of genetic data, such as the UK Biobank, which holds the DNA samples of 500,000 British subjects who volunteered to be included, along with their medical data. However, such risk scores have been slow to become available because of the large numbers of genes involved in each particular condition. For instance, researchers originally thought just 12 genes determined the risk of developing type-2 diabetes. But now, as tens of thousands of people have become enrolled in gene studies and pools of "big data" have amassed, researchers have realized that more than 400 genes play a role in diabetes alone. Encouragingly, the pools of big data on genetics are only growing. The U.S. National Institutes of Health has a Precision Medicine Initiative that looks to collect DNA and health information from one million people, while the Dubai Health Authority plans to create a genomic database of the emirate's entire three million residents. Meanwhile, China, which already publishes about half as many papers about

the CRISPR gene-editing technique as the U.S., placing it second among all countries, also has an extensive gene bank, which includes the genomes of at least 140,000 Chinese people. (*MIT Technology Review*, 4/18; *National Geographic*, 1/19; *Economist*, 1/12/19)

Genetic testing's capabilities are becoming revelatory in terms of not just disease but also in terms of individuals' lifestyle behaviors and habits. Using data from the UK Biobank, along with DNA samples in the possession of 23andMe, the genetic testing company, researchers have found 351 genetic variations linked to when people tend to go to sleep. The UK Biobank includes 85,000 volunteer participants who wear activity monitors, so the genetic data can be paired with reliable measures of what time people are awake and asleep as well as their daily routines of activity. (*New York Times*, 1/30/19)

As such report cards based on genetic information become available, they can be applied to embryos developed via in-vitro fertilization (IVF) in a laboratory dish. For instance, tests are now available to identify those embryos that are at high risk to develop type-1 diabetes or cystic fibrosis, giving parents the option not to select such embryos for implantation. However, this is where such testing begins to encounter challenging ethical implications, as such tests could theoretically allow parents-to-be to select embryos of a particular height, energy level, predicted bedtime or other non-disease-based characteristics. One such test has been shown to accurately estimate a person's full-grown adult height to within 1.5 inches, based on a small DNA sample. In a sign of the direction China may take such research, all of China's athletic hopefuls for the 2022 Winter Olympics will have to undergo genetic screening, according to a document published by the Ministry of Science and Technology. (*MIT Technology Review*, 2/18; *South China Morning Post*, 9/4/18)

" ... and, with the proper medication, they lived happily ever after."

In a previous *inFocus*, we explored the potential for CRISPR, the relatively new DNA-editing technique that can in essence act like a word processor's copy, cut and paste features on sections of DNA. Recently, researchers have learned how to use CRISPR to make DNA edits as small and precise as a single letter of the 6 billion DNA letters (nucleotides A, C, G and T) in a human genome. About 32,000 of the 50,000 changes in the human genome that cause disease stem from variations in a single letter of DNA, or "point mutations." DNA-editing technology would provide a potential pathway to altering, or "fixing," those genes that increase the risk of disease or directly cause particular hereditary ailments (see **inFocus 1105**, 4/27/16; *MIT Technology Review*, 2/18).

It's Getting Personal... and Precise

Genetic testing not only heralds the ability to forewarn individuals of the risk of genetically-related diseases, and perhaps give patients options to treat them, it can also provide doctors with signals about which treatments will work best for individuals based on each patient's unique response to various drugs, an arena known more broadly as precision medicine. One example of this procedure is to sequence the genome of a cancer patient's tumor cells, as is done by the I-PREDICT study at the University of California San Diego. The unique DNA of a patient's tumor can then be compared to thousands of known gene variants and millions of possible drug combinations to predict which cocktail of drugs will best reduce the specific tumor genetics the patient is experiencing, rather than choosing the drug based on which body part is experiencing the cancer. Geisinger, a large healthcare system in Pennsylvania and New Jersey, recently started offering genome sequencing as part of routine preventative care. Part of what genome sequencing can alert doctors to is the identity of certain patients for whom specific drugs don't work as well as they do in the general population, giving them the opportunity to prescribe alternative medications. (*National Geographic*, 1/19)

Genetic sequencing is not the only way to offer patients precision medicine. Researchers have developed two separate approaches to harvesting a patient's cells and then scaling them up quickly in a lab. One way is to use a "plate" that contains 96 tiny test tube wells, each with its own tiny sample of a patient's tumor growing within it. By doing so, doctors can then test as many different drugs or drug combinations on the tumor simultaneously to see how it responds to each. Such testing would then alert oncologists to which drugs are likely to be most effective in treating the patient's cancer, without having to go through a period of trial and error treating the patient with one drug after another. The other way is a similar capability that allows researchers to grow miniature "organs on a chip" that match a patient's various organs, and then to test various drugs on those mini organs before subjecting the patient to them. (*Scientific News*, 1/19/19; *National Geographic*, 1/19)

As humans age, the chances of developing many diseases increase, so that while various global life expectancies have increased dramatically in the past few decades, that aging may be rife with disease. The aforementioned treatments and methods are attempts to offer a wide variety of new options to age more healthfully as well as to live longer. In addition, the aforementioned developments offer a wide variety of new options to help aging populations and those with chronic or serious diseases to get personalized treatment, often more effective than traditional treatments that don't rely on "precision" methods based on an individual patient's DNA and drug metabolism. However, a word of caution is advised, as many of these treatments are in the earliest stage of moving from lab animals to people, and it may be a number of years before they become viable and widely commercially available.

"You've come to a fork in the road—age-defying or age-appropriate?"