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OPINION

Hype vs. hope in medical research

By Eric S. Lander

IS THE PROMISE of genomic medicine overhyped?

This might seem a strange question coming from one of the leaders of the Human Genome Project, and the director of the Broad Institute, which brings together researchers from Harvard, MIT, and Harvard-affiliated hospitals to accelerate the understanding and treatment of disease.

I think the answer is a clear yes — and a resounding no. The contradiction highlights a thorny challenge in the ongoing conversation between scientists and the public.

This summer, I gave a talk at the Aspen Ideas Festival in which I discussed the need to accelerate medical progress through data-sharing and expressed the hope that, within the next 30 to 40 years, we might have enough knowledge to be able to turn cancer, for the majority of patients, into a treatable chronic condition rather than a lethal disease.

I'm always worried about making overly optimistic predictions, but the prospects for major progress are growing.

I was surprised when a reporter for the American Society of Clinical Oncology's ASCO Post later interviewed me about my Aspen talk for its Oct. 10 issue and wondered why I was so pessimistic. Why, she asked, did I think curing cancer would take so long?

To be clear: Science is the most powerful force in the world for improving human health and well-being. It consistently pays enormous returns on society's investment, transforming the way we live and work. It's only natural that expectations run high.

That said, the time frame for the big therapeutic payoffs is often misunderstood.

The scientific path from biological insights to medical impact is often long and winding. It runs from fundamental discoveries arising from basic research, to unraveling the cellular and physiological mechanisms of a disease, to conceiving a "therapeutic hypothesis," to making a drug, to testing its safety and efficacy in humans, to securing regulatory approval. For diseases like HIV and cancer, single treatments rarely suffice: Combinations are needed to forestall resistance.

Progress requires an entire scientific community across academia and industry, with hundreds of contributors supplying both breakthroughs and steady incremental advances.

On occasion, we're lucky, and the work can be telescoped to less than a decade. But luck is not a plan. More often, the pace is frustratingly slow, especially for those of us who suffer (or have friends and loved ones who suffer) from diseases — which is to say, all of us.

Yet if the public overestimates the impact of science and technology in the short run, it underestimates the transformative power over the long run. (This insight is sometimes called Amara's Law, after a 20th-century scientist and futurist.)

After scientists in the 1880s firmly established the "Germ Theory," that bacteria are responsible for some diseases, it took 65 years to understand microbes and to develop effective antibiotics, starting with penicillin. But the Germ Theory's eventual impact was dramatic. Today, we can't imagine the early 20th century — when scrapes might lead to death, ear infections to deafness, and sore throats to rheumatic fever and heart disease. (As an aside, our modern complacency about misusing antibiotics has fueled a growing plague of drug-resistant bacteria.)

Cancer is likely to take at least as long. When Richard Nixon declared a war on cancer in 1971, he imagined an intensive campaign akin to John F. Kennedy's race to the moon. But we had none of the necessities for Nixon's proposed war — no army, no weapons and, most important, not the slightest understanding of the enemy. Though his time frame was misguided, the goal was not. Within a decade, scientists discovered that cancer was caused by mutations arising in our own cells. New kinds of therapies followed, including the first molecularly targeted drugs, in 2001, and immunotherapies,

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in 2011. More than 800 cancer drugs are now under development. Spectacular responses have been seen in previously intractable cancer, such as skin and lung cancer. But they are often temporary, because cancer cells mutate and become drug-resistant. For most cancers, we lack combination therapies with long-lasting effects, such as those we now have for HIV. Nonetheless, the progress is unmistakable. New therapies are appearing at a growing rate, and it's not crazy to think that the pieces might fall together by mid-century.

The Human Genome Project is the case I know best. When we announced, in 2000, the achievement of a rough draft of our DNA sequence, a banner headline in The New York Times proclaimed "Genetic Code of Human Life is Cracked by Scientists." Caught up in the exuberance, some scientists slipped from justified enthusiasm about a major milestone into overpromising about the timing of its consequences.

Many of us tried again and again to emphasize (though we likely missed the mark at times) how much we still had to learn — that the real payoff would be for our children and our children's children.

Nonetheless, expectations rose that cures for most diseases might be around the corner — which, of course, they weren't.

Still, it's amazing what has happened in a mere 15 years. We now know the causes of 4,000 single-gene disorders, and have identified thousands of genes that contribute to genetically complex common diseases, including heart attack, autism, diabetes, inflammatory bowel disease, and Alzheimer's. The cost of genome sequencing has dropped two-million-fold — from $3 billion to $1,500. Genetic analysis of tumors is beginning to become routine as a way to guide cancer treatment. A Battelle Institute report claims that the $4 billion spent on the Human Genome Project has already had an economic impact of nearly $1 trillion.

Schizophrenia illustrates the delicate balance between hype and hope. For more than a century, its biological cause has remained a mystery. Psychotic delusions couldn't be studied in Petri plates or mice. Recently, human genetics has begun to shed light on the disease. An international genetic study of 110,000 participants implicated more than 100 genes, with the largest effect apparently related to overly aggressive pruning of connections between nerve cells during late adolescence. These breakthroughs are exciting because they give glimpses into how schizophrenia develops in the brain. But the insights are still fragmentary, and therapies based on them will probably take decades.

There's the challenge: We need to convey the long-term horizon for transformative impact, while celebrating and sharing advances in research and treatment along the way. We must set ambitious goals that rally scientific energy and action, but not overpromise.

We all need to get better at making the case for realistic optimism. In this regard, we can learn a lot from patients.

Scientists in Boston, including at our institute, recently launched the Metastatic Breast Cancer Project, engaging more than 2,600 patients across the United States to understand this lethal disease. Most know that the chances are slim that the results will transform their own care. But, as a 40-year old mother with terminal cancer told us, "Even if it may not help me, it is going to help somebody. Someday, somebody will get to live with what I have."

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