Genomics and human life span—what's left to extend?

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Publication of the human genome sequence prompted numerous reports of the potential significance of genomics in identifying genetic determinants of rare and common diseases, their diagnosis, and the implementation of new technologies to bring about their eradication. In fact, genomic information may have a much more limited impact on human life span and aging than currently anticipated. In G7 countries, lifetime expectations have increased beyond what had been predicted in earlier reports[1]. In the United States, for example, life expectancy for someone born in the year 2050 is calculated to be 83 years. In Japan, the reports are even more optimistic at 90 years. Indeed, the United States ranked only fifth behind Japan, Italy, Canada, France/Germany (and the UK brought up the rear). Therefore, it appears that by 2050, the affluent populations of the world will have added almost 50 years of life expectancy since 1900.

What additional increases are to be expected from completion of the human genome project (HGP)? The answer is few—and for the following reasons. (1) Genes influencing general health and longevity are many—perhaps hundreds or even thousands and their relation to phenotype is confounded by epistasis and context dependency. Therefore, inferring phenotype from genotype faces a computational barrier that may be transcalculational. (2) The "longevity potential," as far as we know, is found to be distributed equally across a wide variation of genomic types. And (3) if, through molecular genetics, both of our major diseases, cancer and cardiovascular disease, were eliminated tomorrow, the total increase in life expectancy is estimated as less than three years.

This presents the following paradox: HGP is heralded, and funded, on the assumption of its being the greatest potential contribution to human health, anti-aging and, presumably, declining mortality. And yet epidemiological studies now (once again) indicate that longer life expectancy is shaped mostly by a balance between societal resources dedicated to mortality decline, and the effectiveness of those resources[1].

Among epidemiologists the message appears to be that there is simply no causal linkage between genetic influences and population longevity. No doubt, medical care and public health measures have improved, and some of this is connected to gene-based drug design and diagnostics. But, of course, there has been no demonstration that gene variations in the G7 populations, over the short course of time involved in these studies, could account for changes in mortality. In addition, in the first half of the 20th century these same countries added nearly 30 years of life expectancy to their populations, and most of this increase came before vaccinations, before large scale intervention with antibiotics, and before detection of genetic influences of any kind. For all these reasons, improvements in public health resources must be given overwhelming credit for advances in life expectancy.

Recent history of treating cancer and other diseases of aging through gene based technology is not reassuring. A new report concludes that "genomics combined with related technologies of computer aided drug design and combinatorial chemistry linked to high throughput screening" have not improved drug discovery and show little evidence that they will provide the bridge from genome to function even at the level of the protein[2].

These comparisons are not made to belittle the contributions of the HGP and advances in biomedical science; they are to be welcomed. They are made to remind us that miracles of science have played only minor, though heroic, roles in obtaining 50 years of life for potentially all people, that these advances have come mostly from extending to many the conditions of ample nutrition and other public health measures. And they are made to remind us that future applications from technology are defined now in term of providing more and more resources for less and less advance in a span of problematic quality of life. At the same time, of course, all efforts must be continued to understand and prevent, if possible, the many, but rare, single-gene diseases.

One solution to this problem would be to adopt a new more sophisticated approach that is directed to more inclusive goals. Two visionaries have already suggested the forms such an approach could take (both go well beyond but, of course, include, genomics):

> Probably no active, externally imposed program is superior to a system of modification that changes internal incentives and leaves the burden of system improvement to internal processes[4].
> *Urban engineer, Jay Forrester*

> To be enduring, agriculture must imitate the local processes of nature[5].
> *Agricultural pioneer, Wes Jackson*

These overviews have been largely ignored for a quarter century, but are now reappearing, for example, in metabolic control analysis[5,6] which has the goal to "uncover the fundamental design principles. . .underlying structure and function in all cells and microorganisms"[5].

The appeal and wider profitability of this new technology would derive from its realizable goals: inclusiveness and proven effectiveness. In spite of many views to the contrary[7], "complexity" science behind these overviews is sound—metabolic control analysis being only one recent example. Extended to systems of larger scale[8], such a scientific world-view would perhaps allow us to discover constraints at the level of multicellular organisms and of populations that could be violated only with great risk to individual health, to stable ecosystems, to renewable resources, and to sustainable agriculture. If we could find the financial, and other necessary inspiration, and the will to implement the additional research, we would have a science and a technology everyone could invest in.

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1. Tuljapurkar, S., Li, N. & Boe, N.L. *Nature* **405**, 789–792 (2000).
2. Horrobin, D. *J. Royal Soc.Med.* **93**, 341–345 (2000).
3. Forrester, J.W. *Urban dynamics.* (M.I.T. Press, Cambridge, MA; 1969).
4. Jackson, W. *Native to this place.* (Counterpoint, Washington, DC; 1996).
5. Jeong, H. *et al. Nature* **407**, 651–654 (2000).
6. Fell, D.A. & Wagner, A. *Nat. Biotechnol.* **18**, 1121–1122, 2000.
7. Editorial. *Bioessays* **21**, 983–984 (1999).
8. Strohman, R.C. *Nat. Biotechnol.* **18**, 575–576 (2000).