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Personalized medicine or public health? Bioethics, human rights, and choice

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ABSTRACT

The major medical/scientific research project of the past two decades is the human genome project and its suggested clinical applications. The project can usefully be framed as a quest to cure disease, especially cancer, and even to defy mortality. The hero of this quest is the project leader, who currently is trying, almost desperately, to "translate" the science of the genome into public health practice (screening) and the practice of medicine, often termed tailored, precision or "personalized medicine." In America's dysfunctional and patchwork healthcare system, adding another layer of extremely expensive and (to date) marginally effective screening procedures and genetics-based cancer treatments is a hard sell. Nonetheless, framing the human genome project as a quest for added life can make it seem altogether normal, even natural, and can help rally the public to its support. A second, parallel quest is the public health-political quest for a system that guarantees universal access to healthcare for Americans. The ultimate success of this quest will depend not on any scientific or medical breakthrough, even a genetic one, but on political will. Creating and sustaining political support for universal healthcare access will require, I suggest, the deployment of stories of real Americans whose lives have been made much more miserable by the lack of access to decent healthcare. These two quests are converging in ways that may make them incompatible because of the extreme expense of personalized medicine, and, at least so far, its inability to add more than marginal benefit to the lives of most Americans. Nonetheless, until Americans are more comfortable accepting death, we will continue to fight our mortality with activities we frame as quests, making our dysfunctional healthcare system less and less able to respond to the health needs of the American public.

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Medicina personalizada ou saúde pública? Bioética, direitos humanos e escolha

Palavras-chave:
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RESUMO

O Projecto do Genoma Humano (PGH) (*Human Genome Project*), bem como as suas possíveis aplicações clínicas, constituem o maior projecto de investigação biomédica das últimas duas

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décadas. Este Projecto pode ser descrito como uma jornada em busca da cura para a doença (em termos gerais), para o cancro (em particular) e, em última análise, uma tentativa de desafiar a nossa própria mortalidade. O herói desta jornada é o líder do Projecto, que, actualmente tenta, quase desesperadamente, "traduzir" a ciência do genoma para a prática em saúde pública e em medicina, um esforço que é denominado global e genericamente como medicina personalizada. No contexto de um sistema de saúde disfuncional e incompleto como o Americano, é difícil persuadir os cidadãos que é útil adoptarem-se tratamentos e rastreios para o cancro baseados na genética, uma vez que estes são extremamente dispendiosos e apenas (pelo menos à data), marginalmente eficazes. Todavia, enquadrar o PGH como uma jornada em busca de mais tempo de vida pode conferir ao mesmo um cariz de normalidade (quase de naturalidade) que poderá ajudar a mobilizar o público em seu redor. Uma segunda e paralela jornada, esta simultaneamente política e de saúde pública, caracteriza-se pela procura de um sistema de saúde que garanta a todos os Americanos o acesso universal a cuidados de saúde. Ora, o sucesso último desta procura dependerá não de uma descoberta científica ou biomédica, mesmo que esta provenha da área da genética, mas da existência de vontade política. Mais, criar e manter apoio político para o acesso universal à saúde requererá, sugiro, o recurso às histórias de vida dos Americanos reais, que se tornaram tão mais miseráveis pela falta de acesso a cuidados de saúde decentes. Estas duas jornadas têm convergido de tal forma que, devido aos custos enormes da medicina personalizada e, pelo menos até hoje, da sua incapacidade de conferir mais do que benefícios marginais à vida da maioria dos Americanos, elas se tornam hoje quase incompatíveis. No entanto, até que a América se torne mais confortável perante a aceitação da morte, continuaremos a combater a nossa mortalidade com actividades que melhor se caracterizam como jornadas, ajudando a que o nosso sistema de saúde, já de si disfuncional, se torne cada vez menos capaz de responder às necessidades de saúde dos Americanos.

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"The new and rapidly evolving field of genomics offers considerable possibilities for the improvement of human health. . .but the full extent of its possible hazards are not yet fully appreciated."
World Health Organization, *Genomics and World Health*, 2002.

Modern medical research and mass marketing conspire to enable Americans to deny death by suggesting that researchers may yet discover a medical "fountain of youth." Even if the fountain cannot enable immortality, the suggestion is that it will at least be able to postpone death for a very long time. Medical progress itself is now measured almost exclusively by longevity—in terms of both overall life expectancy, but also in terms of survival rates following treatment for disease. Quantity of life continues to be relentlessly pursued and privileged over quality of life. The focus on increasing longevity in medical research is enabled, and even encouraged, by the arts—including classic story telling methods, including the use of the quest myth, and the creative use of metaphor.[1]

In this chapter I examine the application of the quest myth and related metaphors to the most celebrated medical research project of the past two decades, the human genome project, and the ongoing attempt to "translate" genomics into clinical medicine, commonly termed "personalized medicine," and/or public health. These two goals may, however, be incompatible. As James Evans and his colleagues put it in early 2013, "Genomics and public health have been uneasy bedfellows for some time."[1]

Genomic "personalized" medicine

Personalized medicine, medicine tailor-made for each individual patient, has as its premise the belief that an individual's unique genome determines (at least probabilistically) the way the individual will respond to specific drugs, diets, exercise regimes, and other treatment or risk reduction strategies. The goal is often stated as replacing "one size fits all" medicine with "the right drug, for the right patient, at the right time." This is a great oversimplification. What is really at stake is stratified medicine—treating people with similar genetic profiles the same. The most prominent metaphor is to use the individual's DNA, the "blueprint of life," to "tailor" treatment regimes that are most likely to lead to successful treatment—measured in increased length of life, sometimes simply termed "saving lives."[2]

The dream of personalized medicine is largely powered by the successes of the personal computer and the smartphone. Can technology do the same for genome testing by driving down the price and improving the accuracy and speed? By early 2013 the answer is maybe. As explained by an infor-

[1] Portions of this chapter are adapted from and continue the exploration begun in Annas, GJ. Bioethics and genomics. In: Andrew Clapham and Mary Robinson, editors. Realizing the right to health, Ruffer & Rub, 2009, and Annas GJ. The songs of spring: quest myths, metaphors, and medical progress. In: Paul MacNeil, The arts and ethics, Springer, 2013.

mation technologist, "For all of human history, humans have not had the readout of the software [the genome] that makes them alive. Once you make the transition from a data poor to a data rich environment, everything changes."[3] So there is a parallel technological quest, as the *New York Times* suggested in its headline for an article about new genome sequencing machines, to "break the gene barrier."[4]

This quest to cross the gene barrier, of course, immediately suggests the successful quest to break the sound barrier, and even the successful quest to put a man on the moon. President Clinton announced the completion of the first draft of the human genome at a White House event featuring both Francis Collins and Craig Venter in 2000.[5] What has been most commented on is the president's comparison of the map of the American frontier that Meriwether Lewis prepared for Thomas Jefferson, with the "map" of the human genome, which President Clinton termed "the most important, most wondrous map ever produced by human kind." Perhaps he can be forgiven for his over-the-top rhetoric in referring to the code as "the language in which God created life." But Clinton also knew what the public was likely to be interested in:

> With this profound new knowledge, humankind is on the verge of gaining immense new power to heal. *Genome science* will have a real impact on all our lives and even more on the lives of our children. It *will revolutionize the diagnosis, prevention and treatment of most, if not all, human diseases*. In coming years, doctors increasingly will be able to *cure diseases* like Alzheimer's, Parkinson's, diabetes and cancer by attacking their genetic roots...In fact, *it is now conceivable that our children's children will know the term 'cancer' only as a constellation of stars. (emphasis added)*[5]

The precious prize at the end of this quest is the abolition of disease. But when Clinton went off script at the end of the press conference, he reverted to the (American) dream of a longer life: "When we get all this worked out and we're all living to be 150...young people will still fall in love and old people will still fight about things that should have been resolved 50 years ago..." President Clinton can, of course, be forgiven for speaking directly to the public and exaggerating the potential payoff of his federal program. But Francis Collins, the leader of the federal program (he prefers military metaphors, describing himself as the 'field marshall' of the genome project) was just as extravagant when talking about the project to scientists assembled at Cold Spring Harbor just a few months later:

> We have been engaged in a *historic adventure*. Whether your metaphor is Neil Armstrong or Lewis and Clark, *your metaphor is at risk of falling short*. There is no question that *the enterprise* we have gathered here to discuss will change our concepts of human biology, our approach to health and disease, and our view of ourselves. This is the moment, the time when the majority of the human genome sequence, some 85 per cent of it, looms into view. *You will remember this*. You will tell your future graduate students, perhaps even your future grandchildren, that you sat, stood, or sprawled in Grace Auditorium, in the presence of *the intellectual giants of genomics* that fill this hall right now, and of Jim Watson himself, and reflected upon this *astounding time in our history. (emphasis added)*[6]

Although the genome quest is to cure all diseases and lengthen life, there is one constellation of diseases that outranks all others, as President Clinton suggested: cancer. Nor was Clinton alone in highlighting cancer at the 2000 White House ceremony. In the only specific case he talked about, Francis Collins described attending the funeral of "my beloved sister-in-law" (the day before) who "died much too soon of breast cancer." He continued, "The hope and promise of understanding all of the genes in the genome and applying this knowledge to the development of powerful new tools came just too late for her." [5] Craig Venter, in his presentation, went further, noting that the genome sequence represented a "new starting point for science and medicine" with the potential to impact every disease. But cancer was the disease on his mind:

> ...each day approximately 2,000 die in America from cancer. As a consequence of the genome efforts... and the research catalyzed by this information, there's at least the potential to reduce the number of cancer deaths to zero during our lifetimes.[5]

It was, of course, Richard Nixon who launched America's "war on cancer" more than 40 years ago. A decade after the White House genome ceremony, Francis Collins has begun the process of modifying the military war on cancer metaphor described so well by Susan Sontag, to a less ambitious police metaphor:

> Coming like a *thief in the night*, this culprit [cancer] regularly steals away hopes for a long and happy life...But the effort to *catch and convict the culprits* is rapidly gaining ground. The ability to search the genome for both hereditary and acquired mutations provides us with an increasingly precise picture of how these '*genes gone bad*' carry out their *dastardly deeds*. And learning their *MO* provides us with the opportunity to thwart their attacks in much more effective ways, including efforts to *prevent the crime* rather than trying to clean up the mess afterward....'*law and order*' is now a real possibility. (emphasis supplied) [6]

In her best-selling novel, *State of Wonder* (2011), set in Minneapolis and Brazil, Ann Patchett also adopts the quest metaphor, sending her female hero to the remote Amazon jungle to retrieve a precious prize: a drug that would keep ovaries young for a lifetime, and thus permit child bearing at any age. How precious this prize is can be debated, but the historical exploitation of "native" populations for medicines that will benefit only the rich of the world is nothing new. Although it plays no role in the novel, it is worth noting that the US has impinged on Brazil in other ways as well—its companies persuading Brazilians who need their extremely expensive drugs to sue the government to pay the US companies for them under Brazil's "right to health."

The Little Prince's Anti-Quest

Collins also deploys stories (in the science fiction genre) to help explain both why the quest for personalized medicine is slower than he, Venter, and Clinton had predicted, and what the future could still hold should he continue the quest. For example, he concludes his 2009 book, *The Language of Life*, with a chapter entitled "A Vision for the Future." In it he twice

quotes Antoine de Saint-Exupery, the author of *The Little Prince* (which Collins says is "one of my favorite books when I was a child"), "As for the future, your task is not to foresee, but to enable it." [6] But the stories he tells are of most interest. The first story is about a little girl named Hope who was born on New Year's Day, 2000. When she was 20, her favorite uncle died at age 48 of a heart attack. Hope decided to do a complete family history, supplemented with a complete genome analysis (which cost only $300 in 2020). With the assistance of her physician, she learned she was a carrier for cystic fibrosis (CF), and was a higher risk than average for breast cancer and high blood pressure, and at three times the normal risk of a heart attack. These findings motivated her to pay more attention to diet and exercise.

Five years later she met George, who after their engagement agreed to have his own genome analyzed. He was normal for CF, but at higher risk for obesity and colon cancer. When, three years later, they decided to start a family, they did not employ preimplantation genetic diagnosis (PGD), but did have a complete genome screen done on their newborn son, Raymond, aka "Ray of Hope." Ray turned out to be extremely predisposed to obesity (60% probability), and a specific diet with reduced fats and calories was designed for him. By 2035 "all three members of this little nuclear family were doing well." In 2045 George underwent an exam for colon polyps, which were found and removed. "As the years passed, the potential for extending the human life span grew. Hope and George began to explore the possibility of taking a new drug that had just been approved for that purpose."[6]

When Hope was 68 she had a heart attack; but the EMT who responded to the emergency call was able to immediately institute "the proper drug treatment" to save her life because he had access to her genome sequence. The following year George, now 70, developed early signs of Parkinson disease. His physicians used one of his skin cells to grow new neuronal cells to insert into his brain to reverse the disease. In 2100 Hope celebrated her hundredth birthday and she and George their 75th wedding anniversary with their family wishing them "well for many more years to come."[6]

This "dream" scenario is immediately contrasted to a "nightmare" scenario, in which little patient educational material is available and genomic screening is discouraged, so nothing is done after her uncle dies of a heart attack. Hope still meets George and they have a son; but he is seriously obese by age 6 and remains so the rest of his life. Hope herself develops hypertension by age 35. When she has her heart attack at age 50, it goes unrecognized in the emergency department and she dies. Her son is now morbidly obese, and George is unaware that his undiagnosed colon cancer is about to spread to his liver. Collins concludes:

> What a grim scenario! Sadly for us all, this disappointing outcome could still happen. Yes, *medical science, built upon ever-increasing knowledge of the human genome, is poised to deliver substantial medical benefits in the coming years*. Good science is necessary but not sufficient—it will take the full engagement of researchers, governments, health care providers, and the general public to avoid this depressing alternative. (emphasis supplied)[6]

The book ends with a two paragraph "final exhortation." The first paragraph begins by repeating the quotation by Saint-Exupery: "As for the future, your task is not to foresee, but to enable it." This is followed by a plea to readers to help enable his personalized medicine quest: "For the future of personalized medicine, this exhortation is not just for the scientific community, or the medical community, or the government—it is for each of us. The success of personalized medicine will come about only when we each take responsibility for our health." [6]

Using Saint-Exupery's *The Wisdom of the Sands* as a guide to medical research is a surprise. The book is a strange and rambling meditation on life and leadership by an imaginary king of a desert empire. What the king means by "enabling the future" is to ignore it, and work only in the present. The king explains himself in the paragraph before the quotation:

> Then, you may ask me, whereto must I shape my course—since goals are meaningless? And I would answer you by imparting that pregnant secret, hidden under simple, common words, which I have learned little by little in the course of my life: to wit, that preparing the future is but establishing the present. *Those who are forever pursing phantoms of the mind, bred of their imagination, do but fritter themselves away in utopian dreams and vain conceits*. For the true use of the future is to decipher the present... (emphasis supplied)[7]

This view can be seen as an anti-quest view—instead of working toward some imagined, wonderful future, the goal is to concentrate solely on the present. Or, as Saint-Exupery puts it himself (more eloquently and directly): "...all true creation is not a prejudgment of the Future, not a quest of utopian chimeras, but the apprehending of a new aspect of the Present, which is a heap of raw materials bequeathed by the Past..."[7] The major metaphor Saint-Exupery himself uses is that of a gardener who "enables the future" by planting seeds and tending to his garden.

Collins may be on firmer ground with his illusion to *The Little Prince*, which is much better known and is an explicit work of the imagination.[8] Without, I think, falling victim to my own imagination, we can see the little prince's request to the narrator to "Draw me a sheep" as a demand to enable the future by creating something in the present. In the story the little prince is not happy with any of the pictures the narrator draws (just as the grownups were never happy with the drawings he made when he was a child). Instead, it is only when the narrator draws a box and tells the little prince that his sheep is inside of it that the little prince is satisfied: "That's just the kind I wanted."[9]

Perhaps we are like Goldilocks tasting porridge, and searching for one that is not too hot, not too cold, but "just right." Unlike Goldilocks, however, we know at some level that we will never find what we are searching for, but nonetheless believe that the quest itself is intrinsically worthwhile. Or, as the fox tells the little prince in words that could be applied to the leader of the human genome project: "Anything essential is invisible to the eyes...It's the time you spend on your rose that makes your rose important."[10] This, of course, reflects a hyper-individual view of medicine—and seems to ignore population-based public health completely. Can personalized

medicine (aka genomic-based medicine) be reconciled with public health?

What about people who need health care?

The quest for personalized medicine will mean little to most Americans if we are unable to radically reform our health care system, first by making it available to all, and secondly by controlling costs. The "quest" for a robust national health insurance scheme with access for all has been painful.[11] The results, as passed in legislation known as the Affordable Care Act (ACA), are still in doubt, especially following the oral arguments at the US Supreme Court regarding the law's constitutionality in March 2012. At the argument it became clear that at least five of the Justices wanted the US to suggest a "limiting principle" that would allow the Court to find the Act constitutional under the Commerce Clause, but would not commit the Court to finding any other federal requirement that Americans purchase a private product. The argument, including appeals to slippery slopes leading to mandatory purchases of broccoli, cell phones, burial insurance, and even certain kinds of automobiles, was more illuminating in showing commitment to the market as a solution to health insurance coverage than any legal principles. The government's constitutional arguments were just too abstract to defend the constitutional challenge to the ACA. A clear limiting principle is what the Justices wanted, and it was a mistake not to provide one in the administration's briefs (this mistake spelled doom for the administration's reliance on the Commerce Clause, but the ACA was ultimately saved on another ground, the federal tax authority). In the absence of a limiting principle, the uniqueness of the American health care system could be argued best, I think, by illustrating the negative impact of the current dysfunctional health care system on the lives of tens of millions of Americans, and explaining how the mandate makes guaranteed issue of health insurance (regardless of existing health problems) possible, and thus will change their lives for the better. In short, what may have been needed to make the quest for a national health insurance scheme successful (at least for now) is stories.

In electoral politics this is, of course, not controversial. Both President Obama and then Senator Hillary Clinton, for example, recognized the power of individual stories of people whose lives had been dramatically and negatively affected by our current nonsystem on the campaign trail.[2] And after his election, President Obama continued to rely on the stories of real people, including his mother and grandmother, to support the ACA.[12] It is even fair to say that the law, which just barely survived Congress and the Supreme Court, would not have been passed at all were it not for the stories told at a White House summit on healthcare hosted by the President. At the summit, stories of individuals and their often heartbreaking interactions with the health care insurance industry greatly outweighed more abstract arguments about cost and "socialized medicine."[2]

Appellate courts are not supposed to care; but in this case at least an attempt should be made to convince them. And Solicitor General Donald Verrilli finally did on the third day or oral arguments when he made the point I think he could have usefully led with. In his words, focusing on the population of America rather than on individuals, the ACA solves "problems in the economic marketplace that have resulted in millions of people not having health care because they can't afford insurance." Verrilli continued, echoing the health and human rights mantra (that health and human rights are "inextricably linked") in a country without a "right to health":

> There is an important connection, a profound connection between that problem and liberty. And I do think it's important that we not lose sight of that... [because of the Medicaid expansion] there will be millions of people with chronic conditions like diabetes and heart disease, and as a result of the health care they will get, they will be unshackled from the disabilities that those diseases put on them and have the opportunity to enjoy the blessings of liberty. And the same will be true for the husband whose wife is diagnosed with breast cancer and who won't face the prospect of being forced into bankruptcy to try to get care for his wife and face the risk of having to raise his children alone, and I can multiply example after example after example.[13]

The Solicitor General then aptly and succinctly summarized the administration's case that healthcare is unique, and upholding the ACA does require granting Congress unlimited power (the kind that the states have under their "police powers") to regulate Americans under the Commerce Clause. How to deal with the national problem of 50 million people with very limited access to healthcare because they have no health insurance is, he concluded, "a judgment of policy that [non-elected, unaccountable, and way right of center, left unsaid] should respect."[13]

The Solicitor General may well have tried to drag the tens of millions of uninsured Americans before the Court in an act of desperation. Although five of the Justices continue to believe that health care is a private market good, and not a public good, Justice Roberts nonetheless was willing to view the penalty provisions of the ACA as a tax and thus lead a 5 to 4 majority to uphold the mandatory health insurance provisions in the law. Nonetheless, he also viewed the expansion of Medicaid to cover all uninsured poor people as a step too far, ruling that this provision had to be voluntary with each state. Population health care coverage remains a work in progress and its outcome is not predicable at this point. Nonetheless, we can still contemplate the future of genomics as applied to the health of the population of the US.

Competing quests in genomics

It is too soon to tell how either the quest for personalized medicine or the quest for a universal health insurance program will fare in the US. It is not too soon to predict the future if it is "enabled" with successes of both of these quests. The future these twin developments will enable is one in which healthcare costs become the central issue in American healthcare, because by definition using an individual's genome to customize treatment, especially in the realm of cancer (from

which 160,000 Americans continue to die annually), will be crushingly expensive.[3,14]

The dream that even though such treatment will be in the hundreds of thousands of dollars it could turn out to be cheaper than current ineffective radiation, surgery, and chemotherapy seems a complete fairy tale, at least for now.[9,14] To the extent that genomics will make healthcare less and less affordable than it is today, it is more likely that only the wealthy will be able to have access to increasingly expensive drugs and procedures. Public health may make use of genomics—but probably only as inexpensive screening tests. How genomics "fits" is still a work in progress. With whole genome sequencing plummeting in price, there is no doubt that more and more (millions) of people will have their genomes screened at the recommendation of their personal physician. The difficult decisions will not only involve adults (because genomic is probabilistic, heavily dependent on other "epigenetic" factors, and reveals private information not just about the individual, but about their siblings, parents, and children). The much more difficult genomic screening decisions involve fetuses, newborns, and children. Already there is a serious proposal from the American College of Medical Genetics and Genomics for labs to do routine multi-genetic screening of children and adults whenever any particular genetic marker is tested. Similarly, Evans *et al*. have proposed using "public health genomics" to "identify those millions of individuals who unknowingly carry mutations that confer a dramatic predisposition to preventable diseases." How such diseases will be selected for inclusion in population screening, and what the individuals who are identified can actually do to decrease their risk (at least other than diet and exercise) remains to be worked out.

Nonetheless, the bioethics challenge is real: can autonomy (and informed consent) survive the genomic era? Likewise, the human rights vision is clear: will the benefits of genomics be available to all, or only to those who can afford to pay for them with private funds? As James Evans himself has put it, more than 5 years ago, depriving the poor (in any country) of personalized genomic medicine "runs the risk of creating a genetically defined underclass which, because of inheriting more than a fair share of disease-susceptibility genes, is unable to afford adequate medical care."[15]

Conflicts of interest

The authors have no conflicts of interest to declare.

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