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Personalized Medicine

Is it a concept only for the super-rich?

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I read about President Obama's recent call for something he called, "the precision medicine initiative," popularly referred to in the press as "personalized medicine." I did not read the White House's press releases so I may be behind the times. I have read some of the news coverage, and, quite frankly, I'm stunned by the gap between "the cup and the lips." Perhaps "gap" is too euphemistic a term. Chasm or mountain, may be a better description.

The notion behind personalized medicine is reasonable and appropriate for super rich people in the 21st century. The goal is to choose therapies specifically targeted for each individual's illness. If you have a cancer caused by a particular mutation you may be likely to respond to some chemotherapy regimes but not to others. If you have cystic fibrosis, there may be unusual therapies that will work for your expression of the disease. The issue of cost has not entered the discussion, other than to state that the federal government is interested in putting $215 million dollars into the research.

The problem is not the research. In my field, it is likely that within the next decade or two we will have worked out the genetic underpinnings for the major neurodegenerative disorders like Alzheimer's disease and Parkinson's disease, each of which, by the way, has been associated with a large number of individual gene derangements, implying that there are many sub-types of both of these diseases. In the future we may talk about having Alzheimer's type 27 running in a family, as distinct from the other 50 types of Alzheimer's disease. We will hopefully learn, before too long, which of the many different abnormalities that may cause seizures are causing epileptic seizures in our child, which will guide us to choosing the best anti-convulsant drug. These will be wonderful advances, but what will they mean? Every new drug on the market is expensive. In some cases this is because its development required huge outlays and must be recouped, and excesses used to fund future research. In some cases the costs are simply due to lack of competition. When generic drugs suddenly get approved for well known uses, the price may skyrocket a hundred-fold [such as has happened with some drugs for epilepsy and gout], without any justification except the pharmaceutical company could get away with it.

The real problem is money. My patients are increasingly finding themselves unable to pay for their old, generic medications because they have become "tier 2" or "tier 3" drugs, a classification that changes every year. A drug that had required a co-pay of $10 per month is now, commonly, costing $300 per month. Of course, this is for inexpensive drugs. Expensive drugs are a different kettle of fish. These require prior authorization, the bane of most doctors. I can’t blame insurers for putting up hurdles. They want to make the doctor think, or at least sweat and swear, before ordering a drug that costs $5,000/month. Some drugs cost $100,000/year. In general, the fewer the number of patients getting a drug, the more expensive it is. When you’re talking about targeted therapy, you’re talking about very small numbers of patients. This translates into tens or hundreds of thousands of dollars per year, possibly for the rest of one's life, since all of these targeted therapies are treatments, not cures. For example, there are nine immune-modulating drugs approved for treating multiple sclerosis [MS], a disorder that, while uncommon, is not rare. Although one would expect competition to lower

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prices, and perhaps this has happened, the first such drug, approved by the FDA in 1983 and generic for many years, still costs over $4,000/month. In fact, every single one of these MS drugs costs over $50,000/year. However, this is NOT targeted therapy. Targeted therapy would be therapy approved for MS patients who had a particular gene abnormality, thus lowering the number of potential patients, thus increasing the cost. Ten years from now $50,000/year will look cheap.

I am not a medical economist, but I’m not stupid either, and I’m not hiding my head in the sand. Precision medicine will be available soon. It will be the best possible therapy for people who either work in the U.S. Congress and vote themselves the best medical insurance, or are extremely well to do. The costs of these drugs will not be affordable by most wealthy people, however, and will probably be limited to the top 1% or so of Americans. People who make $500,000/year are not going to be able to spend $250,000 of after-tax income every year, often for disorders that will make them unable to make that kind of money any more.

Precision medicine is a nice concept. It is a bioengineering feat that will be attained, but will not serve most of us. Targeted therapy, developing interventions that are generalizable, that can be used to interfere with the expression of bad genes that cause disease, should be the goal, not developing drugs that ameliorate the disorder based on the gene. We want interventions that keep Huntington’s disease from starting, that keep cancer genes from initiating their cascade of events leading to tumors, and not so much drugs that ameliorate but do not prevent or cure. While these interventions will be wonderful for those who will be wealthy enough to receive them, it seems to me that, like so many things, money should be invested more wisely elsewhere. Public health has been, and remains, the most productive investment in medicine everywhere in the world, including the United States.

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Medical matters have been an essential part of the narrative in Downton Abbey, the widely viewed TV series. Downton Abbey strives to be historically accurate in costume, culture and setting over the period it depicts (1912–1924).

Most of the medical conditions are described accurately and contribute to the story line in a historically informed fashion. Conditions such as trauma, PTSD, eclampsia (misdiagnosed, resulting in death), the 1918 influenza epidemic that was more lethal in younger patients, spinal cord contusion (initially diagnosed as a transection) and the question of homosexuality being a disease, were portrayed accurately, concordant with the historical period.

Several significant medical misadventures are worthy of note, however.

The Cook’s Cataract
Early in the series Mrs. Patmore, the beloved cook, underwent cataract surgery. But what is highly sophisticated and safe surgery today was then crude. Dilatation with belladonna dates from 1796 and cocaine anesthesia from 1884, but the incision in the eye was large (compared to today) and patients were thought to require prolonged rest (10 days) after the procedure. However, ambulatory cataract surgery was described by a Dr. HD Bruns (in a little recognized 1915 paper in that pre-information age) in the US with a complication rate of about 7%, no different from hospitalized patients. Before the early 1950s, very thick, heavy eyeglasses were needed after cataract removal, as there was no lens to focus an image. Lightweight plastic eyeglass lenses were introduced only in 1952.

Shortly after World War II Dr. Howard Ridley noted that small acrylic plastic fragments (from fragmented airplane cockpits) that lodged in the eye did not provoke an inflammatory response. He then introduced the first plastic replacement intraocular lens in 1949. However, like hand washing suggested by Semmelweiss (1847), antisepsis suggested by Lister (1867) and H Pylori described by Marshall (1980), this innovation initially was derided and ignored. It took a number of years for the practice to be accepted. Contrast this with the discovery of anesthesia (1846) and X-ray (1895), both of which were accepted rapidly.

The thick spectacles, without which the world would have been only a visual blur for Mrs. Patmore, are absent in all subsequent episodes of Downton Abbey. Without those glasses, however, she could not have continued her cooking career.

The Earl’s Abdominal Pain
In the final episode of the 2015 season set in 1924, the Earl of Grantham develops some intermittent pain in the lower chest and upper abdomen. He is worried about angina and developing a heart attack. After consulting a specialist he is sent for “tests” after which he happily announces that he only has “an ulcer.” In 2015 intermittent chest pain would prompt an urgent cardiac work-up, including a cardiac catheterization if indicated.

The Earl would have had an EKG. In 1918 Guy Bousfield described EKG changes during a spontaneous episode of angina in a single patient with syphilitic aortitis. EKG changes associated with a myocardial infarct were first described by Harold Pardee in 1920. The exercise stress test was first suggested by Wollerth and Wood in 1931 but was thought to be too dangerous. A modified, safer stress test was introduced in 1932 by Goldhammer and Scherf. They also introduced chest leads in 1932 allowing evaluation of previously “silent” areas of the heart. Prior to this, EKG changes in the anterior heart could not be detected. The current lead configuration was initiated in 1942 by Emmanuel Goldberger. Also in 1942 the standard two-step stress test was described by Arthur Master. Thus, in 1924, absent an EKG demonstrating changes in the inferior part of the heart during a spontaneous episode of angina, it would have been impossible to conclude that the Earl’s intermittent pain was or was not cardiac. Interestingly, it was in 1924 that William Einthoven won the Nobel Prize for having invented the EKG some 20 years earlier.

Angina is usually progressive and since the Earl did well without apparent pain between the medical evaluation and the conclusion of the season, many months later, at Christmas, I do not think he had angina (or other, progressive diseases such as cancer or vascular problems).

Today’s patient would then have an endoscopy. But there was no endoscopy in 1924. The Earl probably had an x-ray. An upper GI series (using barium contrast media) with fluoroscopy, then in common use, enabled visualization of the stomach and intestines. Some ulcers could be seen, but not all.

The only treatment for ulcers available to Lord Grantham was diet, antacids and abstinence from “gastric irritants” including alcohol. The Sippy diet, named after Dr. Bertrand Sippy (1866–1924) not because one sipped it, was popular at that
time. It started with milk and cream, taken hourly. One authority suggested carrying a thermos to ease compliance. The diet then progressed to soft or ground food and avoidance of meat, spices and coarse vegetables. Abstinence from alcohol was a part of this larger, more comprehensive regimen. Strict adherence to this program was thought to relieve symptoms in several days but to require several months for actual healing. The Earl declined the strict diet and his only treatment was abstinence from alcohol (until Christmas).

Ulcer pain typically is persistent, burning, gnawing and associated with food, not spasmodic as experienced by Lord Grantham. I suggest therefore that even if he had an ulcer, it is unlikely to be the cause of his pain. The fact that abstinence from alcohol coincided with resolution of the pain does not alter this opinion.

If not angina or ulcers, then what caused the pain? During the one episode of pain caught on camera the Earl clutched his side and the pain was brief. Gallstones are a common culprit in this situation. Many patients with gallstones have isolated episodes of pain and then do well for long periods of time. There were no ultrasounds or CT scans in 1924.

Radio-opaque gallstones can be seen but the gallbladder itself cannot be visualized on a plain x-ray. An experimental intravenous dye, excreted by the liver, that opacified the gallbladder was being investigated in 1924. This initial contrast was toxic. In 1925 safe oral and IV formulations became available and the gallbladder could be seen routinely, though not perfectly [IV and oral cholecystogram]. So even if gallstones had been considered as a cause for Lord Grantham’s pain, there was no way to identify them in 1924. If the illness had occurred one year later in 1925, however, the Earl’s “tests” could have included such imaging. Treatment was available if [radio-opaque] gallstones had been demonstrated and/or his symptoms were very severe and thought, clinically to be due to gallstones. Cholecystectomy was first performed by Langebuch in 1882 and was an accepted procedure in 1924.

Because of the nature of the pain and the clinical course I believe gallstones are the most likely cause of Lord Grantham’s pain. If this smoking gun is pursued in season six with medical complications of the supposed ulcer, I still would not conclude that the Earl’s season five pain was due to an ulcer. Complications of gallstones [pancreatitis, cholecystitis, jaundice, etc], in season six could reasonably be expected however.

The Chauffeur’s Cardiac Condition

In season two, Tom Branson, a chauffeur, is rejected by the British army during World War I because of a cardiac condition. The reason given for his rejection, however, is historically and medically inaccurate. He was told that he had mitral valve prolapse with a pansystolic murmur. But the syndrome of mitral prolapse with a cardiac murmur was first described in 1966 by Dr. John Barlow. The structural abnormality had been known to pathologists, but no clinical correlation had been made.

Cardiac disease was the third-leading cause of disability (after “wounds and trauma” and “chest complaints”) in British soldiers during World War I. In the latter part of the 19th Century it was thought that external forces, such as tight uniforms and heavy packs might be the cause of heart problems. This concept gave way in the early 20th Century to the view that the heart was a machine and that heart disease resulted from global dysfunction and that cardiac dysfunction was not tied to a specific mechanical defect, but rather was manifested by symptoms such as “chest pain, dyspnoea, palpitations on exertion, and tachycardia.” Audible murmurs, clicks and other sounds, in the absence of functional impairment, were felt to be of little significance.

Much time and money were devoted to the study of heart disease in soldiers and a diagnosis of “soldier’s heart” evolved, typified by the symptoms mentioned above. In retrospect, it likely was not due to primary cardiac disease. However, it was thought to be critical to establish criteria for recruits so that men with supposed heart disease were recognized and not accepted.

In 1915 the eminent physician James Mackenzie established written guidelines for the examination of recruits, published by the British War Office. As described by Joel Howell: “MacKenzie saw as the primary issue the functional efficiency of the heart. Murmurs and irregularities were important only if they diminished the functional efficiency. If they did not, and this was to be ascertained either by asking the candidate how much exertion he was accustomed to or by observing him undergoing exertion without distress, then the candidate’s heart was sound and he was fit for duty.” EKGs were not part of this approach.

But even by current standards, the description of Branson’s condition is most likely inaccurate. Mitral prolapse is characterized by a late systolic rather than a pansystolic murmur. It is possible in very advanced disease to have a pansystolic murmur, but these persons are usually clinically ill with dyspnea, fatigue and fluid retention.

As a vigorous, healthy, physically active young man, based on those criteria, Branson would not have been rejected. Rejection for cardiac disease would have been only for a global cardiac dysfunction impairing exercise tolerance, not for asymptomatic mitral prolapse, that, as noted, was not identified as a clinical syndrome until 50 years later.

Generally, the medical issues portrayed in Downton Abbey help us to appreciate our current medical sophistication and shed light on the practice of medicine 100 years ago. The occasional inaccuracies are an opportunity to become reacquainted with a few morsels of medical history. No doubt similar observations will be made 100 years from now as authors then try to recreate our current medical world in future “period pieces.”

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