HISTORY OF MEDICINE

Patenting the PKU Test — Federally Funded Research and Intellectual Property

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In 1960, microbiologist Robert Guthrie and technician Ada Susi invented a bacterial inhibition assay that reliably detected phenylketonuria (PKU) in newborns. The damage caused by PKU, including often profound cognitive impairment, results from an inability to metabolize phenylalanine, an amino acid necessary for protein synthesis and normal growth and development. To be effective, treatment with a low-phenylalanine diet must begin in early infancy, before the onset of irreversible neurologic impairment. Although a ferric chloride urine test for PKU existed in the 1950s, it was unreliable until the infant was 6 to 8 weeks old. The new assay was also more sensitive than the urine test and much easier to administer.

Invention of the "Guthrie test" coincided with both marketing approval of Lofenalac, the first commercially available low-phenylalanine infant formula, and a new national focus on mental retardation. John F. Kennedy, who had a cognitively impaired sister, was determined to make prevention of mental retardation a federal priority, and parents of affected children had begun organizing to promote research on causes and cures. The Guthrie test inspired hope that mental retardation could be successfully treated.[1]

Uptake of the test was rapid. In 1963, Massachusetts mandated screening of all infants for PKU, and other states quickly followed. But efforts to patent and license the Guthrie test generated controversy, a little-known historical episode that presaged current debates over commercialization in biomedicine.

In 1961, the U.S. Children's Bureau (USCB) embarked on a field trial of the test, requiring rapid production of kits to screen more than 400,000 babies. Guthrie, who had a cognitively impaired son and a niece with PKU, was involved in a parents' group, the National Association for Retarded Children (NARC). In consultation with the NARC, he decided that commercial production of test kits would be most efficient.

Guthrie favored the Ames Company, a division of Indiana-based Miles Laboratories, which marketed the earlier PKU tests. Although Guthrie assumed that the government would enter a contract with Ames, the company said it would manufacture the kits only if a patent were issued. In 1962, Guthrie filed a patent application in his own name and signed an exclusive licensing agreement with Miles, under which he would receive no royalties but 5% of net proceeds would be divided among the NARC Research Fund, the Association for Aid of Crippled Children, and the University of Buffalo Foundation (affiliated with the Buffalo Children's Hospital, Guthrie's employer). There was no pricing provision, an omission that Guthrie later deeply regretted.[2]

Miles, however, couldn't quickly produce test kits in the required quantity. So with financial support from the USCB, Guthrie rented a house in which to produce and assemble kits containing the materials necessary to perform and interpret 500 tests, at a cost of about $6 each. But when Guthrie visited the Ames Company in June 1963, he discovered that it planned to charge $262 for what were essentially the same kits. He was appalled, and when appeals to the company proved futile, he alerted USCB officials. They recommended that Miles not be granted exclusive commercial rights, in light of the large public expenditure on the test, the potential effect on states that planned to manufacture their own materials, and the steep price Miles planned to charge. Although the test had been developed with support from various organizations, the majority of the funds had come from the Public Health Service (PHS), which provided $251,700, and the USCB, which contributed $492,000 plus $250,000 through the states, chiefly for the trial. Given this federal funding, the surgeon general of the PHS determined that the invention belonged to the United States and abrogated the exclusive licensing agreement.

This dispute came to the attention of Senator Russell B. Long (D-LA), chair of the Monopoly Subcommittee of the Select Committee on Small Business. In a May 1965 hearing of that subcommittee, Long denounced the award of private patent rights on federally funded research, charging that the "granting of private patent monopolies to the results

Courtesy of the University at Buffalo Archives.

Dr. Robert Guthrie Overseeing a Nurse Administering the PKU Test.

of research paid for by the public is concentrating economic and political power in the hands of a few, is retarding our economic growth, and is stifling our capacity to protect ourselves." He was particularly outraged by such patents in the domain of medical research, declaring, "when the desire to make monopoly profits at the public's expense can adversely affect the health of our children, it is time to call a halt to this immoral and evil practice." Long also noted that under the conditions of his funding, Guthrie had been required to report any invention to the surgeon general for determination of patent-related issues. Yet he had filed his report nearly a year late, well after submission of his patent application. Guthrie insisted that the delay resulted from bureaucratic mishaps, but to Long, it appeared that the report had been "held up for almost a whole year so that a patent could be filed."[3]

The episode was painful for Guthrie, who realized he'd seriously erred in signing the licensing agreement. With politics well to the left on the American political spectrum, Guthrie shared Long's view that government should play a larger role in promoting public health; his belief in government's power to do good was integral to his commitment to universal screening. Distrustful of commercial interests in screening, he never intended to earn anything from the test for himself.

In May 1965, Geoffrey Edsall of the National Institutes of Health (NIH) testified in the Senate hearings that the "granting of such exclusive rights for a device developed with the support of an NIH research grant would be contrary to the spirit — if not the letter — of the unwritten rules that govern the use of such public money." He assumed that this view would be "shared by the majority of scientists, health workers, and educators" and "that most lay persons would take the same position as regards public policy and the public interest."[4]

In reality, there was no consensus in the 1960s on the ethics of privately profiting from research conducted with public funds, and throughout the 20th century, patenting was not uncommon in industry–university collaborations, especially for pharmaceuticals and chemical compounds. Nevertheless, norms governing what should count as a freely available public good have fundamentally changed since 1965.[5]

The shift began in the 1970s, when an "economic competitiveness agenda," prompted by the oil crisis and concern about Japanese competition, began displacing narratives of science's role in fighting communism and defeating disease. During the monopoly subcommittee hearings, the Ames Company's position was vigorously defended by Senator Birch Bayh (D-IN). Although Bayh lost that battle, he eventually won the war: in 1980, he and Senator Robert Dole (R-KS) introduced legislation permitting universities and small businesses to retain title to inventions resulting from federally funded research without obtaining special approval (see Perspective article by Markel, pages 794–796). The Bayh–Dole Act was followed by other bills promoting the commercialization of publicly funded research, a phenomenon soon exported worldwide.

Aggressive commercialization of university research has since become the norm, with universities embracing patenting as an efficient way to transform knowledge into products, generate new income sources, recoup product-development costs, and motivate scientists. This shift in attitudes toward commercialization in biomedicine would probably have been as distasteful to Guthrie as to Long. The story of the Guthrie test reminds us that many clinicians and researchers still find that this "new normal" conflicts with their responsibilities to patients and society, particularly in relation to publicly funded research. The story also underscores how industrial partnerships can go wrong, given the often diverse and conflicting goals of participants. The key principles debated in the Guthrie case underlie the conflicts that remain to this day between political and economic imperatives to commercialize research and the social and moral imperatives to promote public health.

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HISTORY OF MEDICINE

Patents, Profits, and the American People — The Bayh–Dole Act of 1980

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In June, the U.S. Supreme Court issued a unanimous opinion in *Association for Molecular Pathology v. Myriad Genetics* that invalidated the claim of ownership of the *BRCA1* and *BRCA2* genes. On one level, the legal contretemps leading up to this decision grew out of the University and Small Business Patent Procedures Act of 1980, commonly known as the Bayh–Dole Act.[1] Sponsored by Senators Birch Bayh (D-IN) and Robert Dole (R-KS), the law reversed decades of government policy by allowing scientists, universities, and small businesses to patent and profit from discoveries they made through federally funded research — like Myriad's research on breast-cancer genetics, which built on previous publicly funded work and was partially supported by the National Institutes of Health.

The Bayh–Dole Act is beloved by the biotechnology and investment communities. In 2002, the *Economist* called it "possibly the most inspired piece of legislation to be enacted in America over the past half-century" because it "helped to reverse America's precipitous slide into industrial irrelevance."[2] The law certainly contributed substantially to the increase in patents awarded to universities over the past three decades — from 380 in 1980 to 3088 in 2009. More difficult to confirm is industry's estimate that between 1996 and 2007, university-based research-licensing agreements contributed $47 billion to $187 billion to the gross domestic product.[3] Indeed, the law's many critics question how much it has actually benefited the economy (as opposed to individuals and shareholders) and the extent of its social costs.

Nevertheless, many academic researchers assume that Bayh–Dole is an inviolate aspect of doing business. But a review of its origins and consequences supports the idea that policies governing the fast-changing worlds of medicine and biotechnology merit frequent reappraisal and reform.

Bayh–Dole's inspiration was not a perceived need to transform the conduct of research but the economic doldrums of the 1970s. Oil embargoes and the resulting energy crisis, combined with the eroding U.S. automobile, steel, and household-appliance industries, deflated the stock market. Pundits predicted that Japan and Germany would soon rule the world's economy. Adding to this malaise was the fallout of Watergate, the custodial presidency of Gerald Ford, and the Iran hostage crisis.

In 1978, a group of constituents representing Purdue University lobbied Bayh to seek ways of reaping profits from government allocations for university-based research, arguing that although the United States spent billions of dollars annually funding more than half of all academic research and owned 28,000 patents, it had little to show for the investment. There is debate over how many of these patents had been developed into marketable products. Industry representatives insist that less than 5% of all government-funded inventions resulted in licenses for commercial use. But technology-transfer critics argue that the number of patent licenses may be a misleading measure of invention utilization. The Defense Department sponsored the majority of the inventions considered in such estimates, and though contractors could have retained title to the patents, most of these inventions had limited value for the civilian market. In contrast, 325 federal government patents were sponsored by the Department of Health, Education, and Welfare, and 75 (23%) of