Continued advancement of understanding within the natural world has always been driven by the curiosity and intellectual vigor of key characters in history. Our history has been marked with both episodes of fantastic and startling discovery and a multitude of smaller and more intimate moments of insight that couple to advance our knowledge in a steady and seemingly unending progression. The history of medicine has likewise followed this route, where the unquenchable drive to comprehend the seemingly ever more complex human body has been inexorably linked with efforts to develop interventions to ease disease and suffering. No understanding would be possible, however, without the ability to design and perform quality research—research that asks a meaningful question, conducts an investigation in an elegant fashion, and credibly incorporates the outcome into the existing body of knowledge. These tasks are as critical to medicine as performing an exquisite neurological examination or a successful surgery; without such investigative acumen, our knowledge would stagnate and patient interventions would grow old.

Part of the continued training of any physician or physician-scientist is the development of a critical mind and an investigative toolset to conduct pertinent research. As part of this training, one must understand how to ask the appropriate question and to recognize the qualities of a well-designed study. Equally important, particularly in our current time, is the ability to adapt our research to the changing world. As developments push health care toward more personalized medicine (PM) and modernization allows many groups to evaluate the comparative effectiveness of interventions, investigators must tailor their questions to the healthcare reforms around them.

THREE BASIC APPROACHES TO RESEARCH

Clinical or basic science investigations can take a number of different forms, the design of which is driven by a pragmatic end. Any research invariably entails an expenditure of physical and creative resources; thus, the study design should be one that maximizes discovery while minimizing cost, time, danger to both subjects and researchers, and confusion regarding potential conclusions. The approaches to research can be parsed into 3 distinct types: hypothesis driven, discovery driven, and task specific. These 3 types, in a general sense, have been used in this chronological order of presentation, with the hypothesis-driven type the most basic and most rooted in history and the discovery-driven and task-specific forms adopted relatively recently.

The hypothesis-driven research paradigm is familiar to an investigator of any age, from early secondary education on, because of its simple approach and elegant design. Beginning with an observation, a hypothesis is developed to explain the observation, followed by an experimental design to prove the hypothesis and subsequently elucidate the original observation:

Observation → hypothesis → experiment → proof or refutation of observation

Although this method has been used for centuries or longer, it was during the Scientific Revolution that investigators prominently used this deductive type of investigation. Galileo's astronomical observations provided the framework for an experimental design that forever changed our understanding of the natural world (even if, unfortunately for Galileo, these works remained scorned in their time). What cemented the hypothesis-driven investigative technique came later in history with the publication of Newton's *Philosophiæ Naturalis Principia Mathematica* [*Mathematical Principles of Natural Philosophy*], in which, in addition to profound conclusions on planetary motion, gravitational forces, and classical mechanics, he proposed his Rules of Reasoning in Philosophy:

Rule 1: We are to admit no more causes of natural things than such as are both true and sufficient to explain their appearances. To this purpose the philosophers say that Nature does nothing in vain and more is in vain when less will serve; for Nature is pleased with simplicity, and affect not the pomp of superfluous causes.

Rule 2: Therefore to the same natural effects we must, as far as possible, assign the same causes.

Rule 3: The qualities of bodies, which admit neither intensification nor remission of degrees, and which are found to belong to all bodies within the reach of our experiments, are to be esteemed the universal qualities of all bodies whatsoever.

Rule 4: In experimental philosophy we are to look upon propositions inferred by general induction from phenomena as accurately or very nearly true, notwithstanding any contrary hypotheses that may be imagined, till such...

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time as other phenomena occur, by which they may either be made more accurate, or liable to exceptions.

In essence, Newton stated that observed phenomena are explained by simple and generalizable etiologies (rule 1) and that such mechanisms are reproduced throughout nature in a similar fashion (rule 2). Furthermore, he asserted that the results of experimental investigation could be extrapolated to similar phenomena throughout the universe (rule 3) unless proved untrue by another observed phenomenon (rule 4). Newton’s propositions lay the groundwork for all scientific investigation since their original publication in 1713. Today, the majority of National Institutes of Health (NIH)–funded projects are based on the hypothesis-driven approach.

The second basic investigative approach is the discovery-driven method, a process that often entails the collection of massive amounts of data, followed by detailed analysis that looks for patterns of variance among subgroups. The discovery-driven approach is summarized by the “let’s see what happens” attitude or is described more pejoratively as a “fishing expedition.” Compared with the hypothesis-driven technique, the linear algorithm delineated before is set up in a nearly reverse fashion, with the experiment preceding the observation and hypothesis:

Experiment → observation → hypothesis and conclusion

As one can imagine, the physical resources needed for this type of investigation can be immense, with the volumes of data collected requiring subsequent analysis. A relatively recent example of the discovery-driven method is that described by The Cancer Genome Atlas with their pilot study of human glioblastoma specimens. As described by the authors in their 2008 Nature paper, The Cancer Genome Atlas “aims to assess the value of large-scale multi-dimensional analysis of...molecular characteristics in human cancer and to provide the data rapidly to the research community.” Multiple molecular and genetic characteristics were assayed in 206 patient samples with glioblastoma. The subsequent analysis confirmed old notions of glioblastoma multiiforme understanding and enabled the discovery of new mutation patterns and an improved understanding of the molecular basis of disease progression.

The Cancer Genome Atlas serves as the model for many future tumor investigations. Previously impossible feats of genomic proteomic, and epigenetic discovery in wide arrays of sample patients are now possible owing to advances in bioinformatics and molecular techniques. The potential discovery effects are huge concerning both our understanding of disease mechanism and the formulation of targeted therapeutic interventions. As one can imagine, a large number of samples are required to achieve a level of statistical significance when thousands of targets of interest (genes, proteins, etc) are being analyzed. A caveat to the discovery-driven approach is the potential for significant bias within the sample population; any discovery is based solely on the samples that are originally inputted into the analysis, and thus improper screening of these samples can include false-positive specimens and exclude true specimens, which could lead to a false-negative conclusion. Nevertheless, the discovery-driven method is currently receiving increasing funding, particularly because of its potential effectiveness in developing more individualized patient care.

Task-specific approaches are the third type of research technique. They are often the most difficult to design and fund, yet they are the most practical and focused of the 3 methods. In this approach, an investigational device, drug, or intervention must traverse the travails of animal and human clinical trials to prove efficacy. This is the approach used most often by pharmaceutical companies, device manufacturers, and increasingly some NIH-funded ventures:

Hypothesis (intervention/device/drug) → experiment (ie, clinical trial) → outcome

It is a variant of the hypothesis-driven technique but invariably an expensive one. Designing studies that will prove effectiveness yet maintain safety for participants often requires the support and logistics of industry. This is the research style seen most often in neurosurgical settings, where concepts of surgical access (including minimally invasive, endoscopic, and endovascular), ease of use (spinal fixation devices), and patient outcomes (deep brain stimulation technology) are constantly reassessed.

QUALITY RESEARCH

It is one thing to qualitatively describe “good” research: simple, efficient, impactful, and able to withstand the test of time. Yet, simply following the typical paradigms of research design will no more yield a research outcome that is meaningful than a collection of experimental data that are ambiguous or misleading. Many pursuits have ended in failure owing to the inability to properly formulate a precise objective and hypothesis or to an improper or overwhelming experimental process. Through the example of past quality research, we can learn the characteristics that define research efforts that are truly successful and worthy of emulation. The following examples, Watson and Crick’s discovery of DNA structure, the development of statin medications for the treatment of hypercholesterolemia, and finally the role of surgery for single brain metastases, portray aspects of research pursuits that set these studies apart as superior.

THE DNA DOUBLE HELIX

The story of Watson and Crick’s 1953 proposal concerning the double-helix structure of DNA is well known, and despite the passage of more than half a century, their work continues to be emulated in modern science. The 25 years before their publication saw great advancements in the understanding of genetic heritability; a series of elegant studies had strongly suggested that DNA constituted the
“substance” within organisms that carried genetic information. The scientific world was hardly convinced, however, and many great names of the day still considered that proteins were the likely molecular agent that encoded genes. A key notion preventing wide acceptance of the DNA heritability theory was the view that DNA was too simple, for biologists doubted that a molecule with only minor variations (i.e., a choice of 1 of 4 nucleic acids per deoxyribose moiety) could possibly provide for the immense complexity required for heritability in larger organisms. Watson and Crick formed their working alliance because of their independently derived suspicions that DNA was indeed the answer. Working with this hypothesis, they also surmised that if they could unravel the structure of the DNA molecule, then they would also realize the coding pattern of genetic transfer. Working in collaboration with colleagues at Kings College, including x-ray crystallography experts Gosling, Wilkins, and Franklin, the 2 researchers inferred DNA structures through interpretation of x-ray diffraction films coupled with 3-dimensional models constructed within the laboratory. Their final model was a double helix of 2 intertwined antiparallel phosphate-sugar backbones, with complementary nucleic acids facing inward and joined by hydrogen bonds. The 1953 article, published in Nature, featured the relatively nonchalant line “This structure has novel features which are of considerable biological interest,” a considerable academic understatement. The article, totaling only a single page, stated simply the solution to a problem that had vexed the scientific community. Furthermore, with the equally modest line, “It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material . . . .” the authors tackled the concept of transfer of genetic material. The DNA double-helix proposal justified and incorporated a large amount of current scientific knowledge while propelling the fields of molecular biology and genetics toward new discovery.

The double-helix concept withstood decades of scientific scrutiny until more conclusive experiments with improved imaging technology finally confirmed the structure. Based on the double helix and the investigators’ suggestions for a gene transfer mechanism, countless advancements were made in the understanding of genetic replication, transcription, and mutation analysis. A multitude of academic pursuits were influenced, including molecular-based medicine, law, and forensics and computational science. The story of the DNA double helix keenly illustrates the traits seen in high-quality research, including synthesis of collected data, verifiability of proposed mechanisms of action, and extrapolation of the results to other investigative pursuits.

**HMG CoA REDUCTASE AND STATINS**

A hallmark to the success of unraveling the DNA double-helix structure was the collaboration of multiple, and sometimes competing, investigators who shared a common goal. Another example of the benefits of superb collaboration and communication leading to a remarkable investigative outcome is that of the identification of the HMG-CoA reductase enzyme as a therapeutic target for hypercholesterolemia. The rapidity of discovery concerning cholesterol biosynthesis during the early latter half of the 20th century enabled efforts to pharmacologically alter the pathway and thus reduce low-density lipoprotein (LDL) levels in patients at atherosclerotic risk. Through the efforts of 3 men, Joseph Goldstein, Michael Brown, and Akira Endo (working independently), basic science revelations were translated to drug delivery in the clinical setting, and millions of patients have benefited from LDL lowering through statin therapy. Their collaborative story is a key example of basic science enabling translational discovery and arrival at a successful clinical intervention.

Goldstein and Brown began their work on the broad shoulders of previous biochemists who had elucidated the cholesterol synthesis pathway. It was known that HMG-CoA reductase was the rate-limiting enzyme, yet the mechanism for intrinsic control of enzymatic activity was unknown. Through their work with patients suffering from the autosomal dominant disorder familial hypercholesterolemia, the 2 surmised that another control protein, possibly a yet-to-be-discovered cholesterol transporter, was responsible for the elevated LDL cholesterol phenotype. Their landmark article demonstrated both that the HMG-CoA reductase was indeed normal in the affected patients and that the enzyme was constitutively active in their patients owing to the failure of feedback suppression by LDL. Their further work regarding the pathways of cholesterol transport and metabolism was notable for a number of groundbreaking discoveries, including characterization of the LDL receptor, receptor-mediated endocytosis, receptor recycling, and feedback regulation of receptors.

The statin class of medications uses the feedback regulation of receptors to selectively lower circulating LDL levels (and the subsequent incidence of atherosclerotic thrombi). Through statin-mediated competitive inhibition of HMG-CoA reductase, liver cellular cholesterol production is decreased. Hepatocytes respond by increasing the number of surface LDL receptors, thereby maintaining normal hepatic cholesterol levels while decreasing circulating LDL. This revolutionary class of drugs would not have been possible without the persistence of Akira Endo, who painstakingly isolated the first statin, compactin, from a library of fungi in his laboratory. The proof for likely clinical benefit would come from his collaboration with Goldstein and Brown, when he generously supplied compactin for testing in their familial hypercholesterolemia cell-based assays. The world knows of this work today because of the subsequent investment of the pharmaceutical industry in transforming molecular cousins of compactin into the ubiquitous statins, a medication prescribed to all of those at increased atherosclerotic risk and credited with vastly reducing death resulting from heart attack and stroke.
The story of Goldstein, Brown, Endo, and statins is one that has become rarer today in an era ripe with basic science research but lacking in the ability to get discovery to the clinical setting. The success of the discovery of statins was due to excellent basic science research, laboratory collaboration, open communication, and finally the push toward drug refinement and development in the industry setting. Despite large increases in expenditure for basic science investigation at the NIH and in research and development at pharmaceutical companies, the output of new drug agents has slowed in the past few decades. The reason is likely multifactorial, from the divergence of the “physician-scientist” to the “physician and scientist” who do not communicate well to research grants that recognize publication merit over clinical applications of outcomes. The result is the creation of a “valley of death” that persists between the bench-to-bedside applications. To cross this hindrance, federal entities are now beginning to invest in translational science, training individuals and centers to bring encouraging findings into the clinic. There is hope that new investment by the NIH in their Clinical and Translational Science Centers will spur this type of crossover, but with translational funding topping out at 2% of the current NIH research budget, it may be many years before any outcomes are seen from this investment.

SURGERY FOR SINGLE BRAIN METASTASES

Scientifically rigorous prospective trials in neurosurgery are inherently difficult to conduct because of the vulnerability of patients and invasiveness of procedures. No surgical field is more ripe for the characterization of optimal interventions owing to the rapid increase in treatment-type availability during the past few decades, including endoscopic, endovascular, minimally invasive, and functional surgeries. A well-designed study can change the clinical practice of an entire field, as was seen with the 1990 publication by Patchell et al of a prospective randomized trial of surgical treatment of single metastases to the brain. Before this publication, practitioners were formulating treatment plans based on a scattering of retrospective studies, which were plagued by bias in patient selection and physician preferences. Identifying the need for firm evidence of intervention type in a clearly demarcated patient set, the trial investigators formed a well-characterized set of inclusion and exclusion criteria and posed a simple question of efficacy of surgical tumor resection in addition to the established treatment of whole-brain radiotherapy. Their outcomes were clear and convincing, supporting surgical intervention for its benefit of reduced local recurrence, length of survival, and length of functional independence without increasing morbidity.

The single brain metastases investigation confirmed that well-designed neurosurgical clinical trials are possible and can be transformative. Current neurooncology reviews 2 decades since the Patchell et al publication continue to cite its findings as guiding principles for patients meeting inclusion criteria. The study is one to emulate for its ability to withstand the test of time and capacity for consistent and reliable clinical application. Both before and since its publication, other randomized trials in neurosurgery have proceeded, and their outcomes have been highly influential on the field. All are evidence that such prospective, randomized, and blinded trials (when possible) can clearly justify their costs and efforts.

RESEARCH IN AN AGE OF MEDICAL REFORM

The type and scope of quality research are highly influenced by the state of the world at large, with healthcare patterns, media communication, and tidal-like ebbing in public and professional interests directing the scope of scientific investigation. The above example of the development of the first statins took place in a time of rapid growth of the pharmaceutical industry and improved understanding of modifiable risk factors for cardiovascular health. The type of research that will and should be conducted in the current neurological environment is equally affected by the trend of current healthcare practice and health-related legislative trends. Two major reforms are sweeping through medicine today, comparative effectiveness research (CER) and PM, and guiding our research along these avenues should produce increased opportunities for funding and the ability to influence the conduct of clinical practice.

Comparative effectiveness research is defined as research designed to inform healthcare decisions by comparing the effectiveness, benefits, and harms of various interventions, diagnostics, and preventive and health monitoring strategies. It is a relatively new concept arising from 2 competing developments in medicine during the past decades: (1) the rapidly expanding treatment discovery and associated medical technology leading to multiple strategies of intervention for a single disease and (2) the associated ballooning of cost (in patient risk, failure of benefit, and dollar investment) for medical care. Advocates of CER describe this research as essential in providing an honest head-to-head comparison of interventions, not only for the average patient but also for unique and minority patient groups. Funding for CER has skyrocketed recently, mostly because of a rapid infusion of federal funding at the end of this last decade. Of the more than $700 billion granted by the American Recovery and Reinvestment Act during this most recent economic downturn, approximately $1.1 billion was specifically allocated to “patient-centered outcomes research.” The funding was divided between multiple existing agencies, including the NIH, the Agency for Healthcare Research and Quality (part of the Department of Health and Human Services), and the Veterans Administration, all of which had some experience with the decision and implementation of CER. As part of its mandate, the American Recovery and Reinvestment Act established the Federal Coordinating Council for
Comparative Effectiveness Research. This council was tasked with optimizing strategies for the coordination of CER and has since had a role in developing areas of key interest for emphasized funding. These 100 topics of special importance were selected through input from medical professionals and the public and represent high-value topics that could benefit from head-to-head trials of diagnostics and therapeutics, analysis of health information delivery, and characterization of effects on vulnerable population groups.\textsuperscript{15,16}

Neurological and neurosurgical topics feature prominently within these 100 subjects. A brief review delineates 5 areas that deal specifically with surgical intervention for spinal orthopedic and neurological disease, including low back pain, spinal deformity, cervical spondylotic myelopathy, and cervical disk pathology (Table).\textsuperscript{17} Other topics address neurological conditions in which neurosurgeons could feature prominently, including selection of imaging modalities for general cranial neurological conditions and pharmacotherapy for epilepsy. A review of CER proposals currently receiving funding shows a relative dearth of neurological and neurosurgical attention than would be hoped for and expected given their aforementioned emphasis, with \(<2\%\) of all proposals studying brain or associated conditions.\textsuperscript{18} The opportunity is ripe for neurosurgeons to take the lead and both guide federal research funds toward the field and shape the context of treatment interventions.

Two neurosurgery-related CER types are investigations designed to generate evidence of new effectiveness of an intervention and investigations conducted in silico in which researchers conduct a meta-analysis of all trials to determine benefit or harm for population subgroups. An example of the first such type of study was conducted within our own department; we examined surgical outcomes in a matched population undergoing craniotomy with conscious sedation (awake craniotomy) and general anesthesia.\textsuperscript{19} Although most outcome criteria were statistically similar, patients in the former group enjoyed a shorter hospital stay (3.5 vs 4.6 days) than those enrolled in the general anesthesia group, resulting in diminished healthcare cost without the sacrifice of increased surgical morbidity. Studies of this nature can alter patterns of clinical practice and guide a field toward optimized and more efficient therapeutic strategies.

The second type of CER strategy is more commonly called a research review, a systemic analysis of existing evidence. These reviews benefit from both a larger cumulative population of enrolled subjects and a likely greater diversity of participants owing to the expanded geographical catchment that multiple studies offer. There is a recently published example within the Cochrane Database comparing outcomes from patients with brain metastases treated with whole-brain radiotherapy and whole-brain radiotherapy combined with stereotactic radiosurgery.\textsuperscript{20} The authors identified 3 randomized controlled trials that met their established study criteria and concluded that combination therapy did not benefit patients with multiple lesions but did result in longer survival, decreased local recurrence, decreased steroid use, and improved daily function in patients with a single metastasis. Such study reviews can more directly address the question of clinical harm or benefit for subgroups of patients who were missed as a result of underpowered primary studies.

Expanding the idea of CER beyond optimization of health strategies, critics and proponents cite its potential effect on reimbursement rates and practitioner/patient selection of intervention. In an era of rapidly rising healthcare costs, both private and federal health insurances are demanding CER to justify costly interventions that may not provide any relative benefit compared with more conservative measures. One article describes a “pay for effectiveness” strategy\textsuperscript{21} in which equally efficacious interventions would receive identical reimbursement, regardless of upfront cost, thereby naturally selecting for the lower-cost option. Similarly, procedures, drugs, or devices with superior outcomes would receive reimbursement at a higher rate. To allow medical innovation, there would be a defined time limit for reimbursement, requiring that CER prove advantage over existing modalities to allow continued reimbursement. If one applied this scenario to the last decade of neurosurgical progress, then procedures such as endoscopy and minimally invasive spinal fixation would not receive reimbursement. Therefore, it is imperative for neurosurgeons to lead this type of research effort to have the opportunity to help shape the healthcare agenda.

Personalized medicine is the other major reform driving the evolution of current healthcare. Often described as “the right treatment for the right person at the right time,” the concept of PM has grown directly with an increased understanding of disease mechanism and realization of subgroup variations in molecular and genetic profiles. Genomics and proteomics have created an avenue for characterization of an individual’s susceptibility to disease, response to medical or surgical intervention, and expected adverse events, all with the goal of improving health outcomes.\textsuperscript{22} This type of individualization affords a new type of health maintenance and treatment, called P4 medicine, that is distinct from the reactive type of medicine practiced in the past. P4 medicine has 4 attributes: It includes a personalized approach that takes into account a person’s genetic profile, is predictive by anticipating susceptibility to disease and response to treatment, is preventive in its focus on maintaining wellness before disease strikes, and is participatory by empowering patients to take more responsibility for their own healthcare.\textsuperscript{23} The economic potential for a P4-type healthcare system is estimated to be massive. Including factors that are both internal and external to the traditional boundaries of US healthcare, the PM market is estimated at $232 billion currently and is expect to grow by 11% annually.\textsuperscript{22}

Current neuroscience research practices should evolve with the expansion of PM. Funding sources will rate highly
investigations that include a personalized component. A good example is the changing understanding of subtle molecular mechanisms of high-grade gliomas and relative resistance to medical therapeutics. Despite a universal poor prognosis, survival patterns show impressive variability despite identical treatments with surgery, radiation, and alkylating chemotherapy (ie, temozolomide). Improved molecular characterization of refractory versus responsive tumors has highlighted the importance of alkylate resistance via direct DNA repair by O6-methylguanine methyltransferase (MGMT) and concurrent improved progression-free and overall survival in patients with highly methylated MGMT promoter sequences. Clinical studies have established tumor MGMT methylation status (as assessed by rapid molecular techniques) as an independent prognostic factor for patient survival when treated with an alkylating agent.\(^{24}\) As a result of these findings, efforts to modify MGMT-regulated resistance have proceeded, including identification of MGMT substrate inhibitors (ie O6-benzylguanine) and RNA interference gene silencing. There are undoubtedly dozens of other high-grade glioma variations that alter treatment response patterns, and they should constitute an area of active investigation. Expanding on this theme, a PM approach to neuro oncologic disease should take advantage of finding biomarkers for more aggressive tumors and identifying treatments that exploit the intrinsic heterogeneity of tumor cells.\(^{25}\)

The state of healthcare practice and delivery is on the cusp of a paradigm shift, from a traditional “reactive” method to a more nuanced approach based on prevention and a fluid strategy of treating disease with therapy titrated to the individual patient. Comparative effectiveness research and PM are here to stay, and the neurosurgery field needs to embrace these reforms for the opportunities they present. We have highlighted these reforms, together with providing examples of quality research, to invigorate current and future investigators toward conducting meaningful, impactful, and patient-related research.

**Disclosure**

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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