

Review

The role of evidence-based medicine and clinical trials in rare genetic disorders

Kruer MC, Steiner RD. The role of evidence-based medicine and clinical trials in rare genetic disorders.
Clin Genet 2008: 74: 197–207. © Blackwell Munksgaard, 2008

The drive to empirically evaluate and analyze tools for the screening, diagnosis, management and monitoring of disease captured by the phrase ‘evidence-based medicine (EBM)’ has firmly entrenched itself as part of standard clinical care. However, rare genetic disorders, by their very nature, challenge the generation and application of EBM. This review presents many of the challenges encountered in applying EBM to rare genetic disorders, highlighting areas of recent emphasis in establishing multi-institutional collaborative research networks and in the systematic evaluation of developing therapies. Resources for identifying EBM tools for the practitioner are discussed, and the features and limitations of such resources are presented. Although the application of EBM to rare genetic disorders has definite limitations, a foundation has been established, and ongoing efforts seeking to systematically summarize and critically evaluate available evidence will continue to help identify the most effective tools for screening, diagnosis, management, and monitoring.

MC Kruer^{a,b} and RD Steiner^{b,c,d}

^aDivision of Pediatric Neurology and Division of Developmental Pediatrics, ^bDepartment of Pediatrics, ^cDepartment of Molecular and Medical Genetics, and ^dOregon Clinical and Translational Research Institute, Child Development & Rehabilitation Center (CDRC), Doernbecher Children’s Hospital, Oregon Health & Science University, Portland, OR, USA

Key words: clinical trial – evidence-based medicine – genetic – rare disorders

Corresponding author: Robert D. Steiner, MD, CDRC-F, OHSU, 707 SW Gaines Road, Portland, OR 97239, USA.

Received 16 January 2008, revised and accepted for publication 21 April 2008

Evidence-based medicine (EBM) refers to the concept of using empirically collected evidence to guide clinical decision-making and was operationally defined by Haynes (1) as ‘a set of tools and resources for finding and applying the current best evidence from research for the care of individual patients’. The EBM movement arose from a desire to render medical practice more objective, seeking to prevent unhelpful and/or potentially harmful treatments and practices from being perpetuated. Proponents of EBM attempt to objectify medical practice through use of the best available, most rigorously tested screening, diagnostic, management, and monitoring approaches. EBM has also been employed in analysis of the cost-effectiveness of differing approaches to diagnosis, screening, and management (2).

Although it has become firmly established within contemporary medical practice, EBM does represent a departure from traditional clinical

medicine, which relied on pathophysiologic theory as its foundation, coupled with the individual physician’s experience and clinical judgment (3). At its philosophical foundation, EBM represents a biomedical extension of empiricism (4), seeking to objectively evaluate diagnostic and treatment modalities in as unbiased a manner as possible, independent of current pathophysiologic theory and clinical experience (which, it has been argued, are inherently biased). EBM attempts to make observations based upon studies that compare groups of patients to ‘average out’ their differences. Studies are then stratified by categorizing the relative strength of each study.

Criticisms of EBM are summarized in Table 1. Opponents of EBM point out that physicians treat individual patients, not populations, for which trends may not apply. In addition, critics also note, with some irony, that the application of EBM to clinical practice is not, in itself, evidence

Table 1. Criticisms of evidence-based medicine (EBM)^a

The applicability of EBM to individual patients is limited
 EBM is not itself evidence based
 EBM limits the physician's autonomy
 EBM's definition of acceptable evidence is narrow
 Empiricism, from which EBM is derived, represents a poor philosophical basis for medicine

^aDerived from Cohen et al. (2004).

based; that is, studies have not shown that practitioners of EBM make better physicians (5). Some believe that EBM may lead to a loss of clinical acumen by pushing many physicians toward a formulaic 'consensus' approach to clinical problems and away from personal critical and deductive thinking (6–8). In addition, the application of EBM may certainly be taken to extremes (9), for example in the scenario wherein clinicians might withhold potentially useful therapies with an acceptable side effect profile solely because evidence does not yet exist to support their use. Many physicians and investigators have rejected the empiricist notion that EBM should be practiced independently of pathophysiologic theory, pointing to predicaments in which appropriately designed randomized controlled trials have nevertheless come to completely opposite conclusions (10). More recently, EBM advocates have called for the integration of EBM and biomedical theory, wherein evidence-based studies may be suggested by prevailing theory, and theory may be reworked if the available evidence suggests otherwise (1). Although this balance may be the most appropriate approach to achieve excellence in clinical practice, the integration of these two disparate philosophies, however, remains imperfect (11).

Despite its limitations, EBM has blossomed since the seeds for its development were planted in the 1970s in the writings of Archibald Cochrane and established by faculty at McMaster University. The ability to refer to available evidence to guide decision-making in clinical 'gray areas' has generally been well received by clinicians. In addition, careful review of the evidence may facilitate decision-making when several therapeutic options are available, allowing clinical acumen and autonomy to continue to play a central role in patient care.

Central to the idea of applying EBM is the need for thorough review and appraisal of available literature by the treating provider. EBM stratifies available evidence into discrete categories, placing more weight on those in which sources of bias have been systematically minimized. The prospective, placebo-controlled, randomized clinical trial (RCT) is thus afforded the greatest weight, while case reports are given the least (Table 2). Several

Table 2. Levels of evidence^a

Level I: Evidence obtained from at least one properly designed randomized clinical trial
 Level II-1: Evidence obtained from well-designed controlled trials without randomization
 Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group
 Level II-3: Evidence obtained from multiple time series with or without intervention. May also include dramatic results in uncontrolled trials
 Level III: Case reports, case series, expert opinion or consensus panel

^aDerived from U.S. Preventive Services Task Force.

national and international organizations have taken up the task of summarizing, evaluating, and contextualizing the available evidence to make it more accessible to providers. The Cochrane Collaboration's systematic reviews serve as a well-established model in this endeavor (12). Furthermore, in the field of rare genetic diseases, because fewer studies are performed, comparatively, practice guidelines and systematic reviews often remain relevant for a longer period of time, although there are few Cochrane reviews published on rare disorders.

Instruction on the critical evaluation of published medical research has been integrated into core curricula in medical schools and residency programs throughout North America (13, 14). However, despite an increasingly savvy population of consumers of the published medical literature, significant challenges remain in the application of EBM to the practice of clinical medicine. In fact, within the microcosm of rare genetic disorders, many of the fundamental controversies surrounding the benefits and limitations of EBM are particularly evident.

Should EBM be applied to rare disorders?

Derived from epidemiologic roots, EBM is particularly well suited to detecting differences between large cohorts. However, these differences may be obscured if heterogeneous groups are recruited or if inadequate sample sizes are available. Both problems are particularly salient in the study of rare disorders. As discussed above, the generalization of findings from large cohorts to individual patients is also not always appropriate. However, clinicians' ability to diagnose and treat rare genetic disorders has grown significantly, and objective tools to evaluate such interventions are urgently needed. In this way, EBM may fill an important niche, although an awareness of the limitations of EBM is certainly called for.

Challenges in applying EBM to rare genetic disorders

Few patients are affected by rare genetic disorders

First and foremost, the label 'rare genetic disorders' challenges the application of EBM (15), which, by design, is comprised of evidence that gains strength as it accumulates statistical power. One can be increasingly certain of an effect, or lack thereof, as sample size increases. Populations of individuals affected by rare genetic disorders are inherently small pools from which to draw, challenging investigators in the design of appropriate clinical trials. A recently proposed solution in the field of inborn errors of metabolism (IEM) was the establishment of multi-institutional, collaborative clinical research networks to investigate both natural history and potential treatments (16), and efforts toward this end continue. A few notable collaborative networks have been successfully established that include rare disorders (Table 3). However, such collaborative networks have been slow to materialize, likely because of a number of factors, including the

non-trivial issues of financial support, infrastructure, and the number of competing demands placed on a clinical investigator's time (17).

A small number of medium-sized, single site trials of treatments for rare genetic disorders have been successfully initiated and completed, including a recently completed trial of dichloroacetate (DCA) for the treatment of congenital lactic acidosis (18), demonstrating that such trials are feasible. This study has shown an effect of DCA on lactic acid levels (a surrogate end point) but not on overall clinical/cognitive outcomes, the trial's primary end point. However, in the case of this trial, accumulating a significant number of subjects at a single institution necessitated the inclusion of a heterogeneous mix of disorders with a common biochemical abnormality, lactic acidosis. This trial illustrates one of the difficulties in applying EBM to rare disorders, that of subject heterogeneity. One also wonders if individual disorders within this mix might have shown a more robust and measurable clinical response to DCA, arguing for the necessity of collaborative efforts.

Table 3. Collaborative research networks (a few international examples followed by US NIH-sponsored networks) that support rare disease research

International
Cooperative International Neuromuscular Research Group (CINRG)
Cystic Fibrosis Foundation and Patient Registry (PORT CF)
Duchenne Research Collaborative International (DRCI)
National Cancer Institute
Children's Oncology Group (COG)
Pediatric Brain Tumor Consortium (PBTC)
National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
Childhood Arthritis & Rheumatology Research Alliance (CARRA)
National Heart, Lung, and Blood Institute
Comprehensive Sickle Cell Centers (CSCC)
Transfusion Medicine/Hemostasis (TMH) Clinical Trials Network
Thalassemia Clinical Research Network
Pediatric Heart Network (PHN)
National Eye Institute
Pediatric Eye Disease Investigator Group (PEDIG)
National Institute of Child Health and Human Development (NICHD)
Birth Defects Initiative and Research Network
National Institute of Neurological Disorders and Stroke, NIAMS, NICHD
Muscular Dystrophy Clinical Research Centers
NIH ORD and others
Rare Diseases Clinical Research Networks (RDCRN)

Notes

1. For most networks, only the major sponsor is listed
2. This list is just a sample of such networks and is not intended to be a comprehensive list
3. Although most of these networks are United States based, many have international sites

The future of the RCT in rare disorders

Ongoing efforts may still reap the benefit of pooled resources built upon a collaborative, multi-institutional framework. Professional meetings are a natural forum in which to cultivate such a network, and to this end, workshops held at the American College of Medical Genetics annual meeting, sponsored by the US National Institutes of Health (NIH), have focused on establishing such networks and pushing forward vital research on rare genetic diseases since 2003. In addition, the NIH Office of Rare Diseases (ORD), in collaboration with the National Center for Research Resources (NCRR) and several other institutes of the NIH, established the Rare Diseases Clinical Research Network (RDCRN; 19), which supports multi-institutional, collaborative efforts aimed at facilitating research on rare diseases. Although based in the United States, the RDCRN includes several international sites, primarily in Canada and Europe. Several longitudinal and natural history studies as well as clinical trials born out of these efforts are currently underway. In the UK, the national Medical Research Council has committed its support to rare disease research by funding the development of patient cohort registries (20). Internationally, the cystic fibrosis registry (PORT CF; 21, 22) has successfully established an international collaborative database involving 172 centers through which clinicians and researchers can enter and share data in real time. Such

a paradigm might serve as a useful large-scale model from which to develop future programs. Despite the key role that disease registries and support groups may play in the generation and dissemination of research advances, many such registries are supported by industry sponsors. For example, registries for some of the lysosomal storage diseases are sponsored by the biopharmaceutical firms that developed and dispense enzyme replacement therapies. Such sponsorship may be construed, rightly or wrongly, as a potential conflict of interest in the setting of attempts to generate and disseminate objective, impartial evidence.

Areas of controversy are being actively addressed through concerted calls for program development, such as the recently issued US NIH National Institute of Child Health and Human Development (NICHD) National Coordinating Center for Newborn Screening Translational Research Network (NBSTRN). Table 3 lists a number of research networks, many but not all US NIH sponsored, that each support clinical or translational research in rare diseases.

When evaluating the strength of various forms of evidence (Table 2), multi-center trials are weighted more than single site trials, in part because the demonstration of efficacy in more than one center implies generalizability. Such efforts thus have the ability to powerfully affect the evidence base available for a given disorder. As evident from the table, however, efforts toward the establishment of collaborative networks supporting research in rare diseases remain somewhat fragmented, incomplete, and in some cases, duplicative.

Support for collaborative efforts in rare genetic disease diagnosis and patient education is also being fostered. In particular, the Collaboration, Education, and Test Translation (CETT) program (23), supported by the ORD, has already launched programs for several rare diseases. The CETT is a multidisciplinary program that seeks to foster collaborations among medical geneticists, genetic counselors, researchers, advocacy groups, and Clinical Laboratory Improvement Amendments-certified laboratories to streamline the diagnostic process, promote the collection of genotype-phenotype data, and disseminate the most up-to-date diagnostic and prognostic information to affected patients and their families. Securing future grant support from foundations as well as government sources such as the US Federal Drug Administration (FDA) Office of Orphan Product Development will be instrumental in supporting future RCTs initiated by investigators in the medical genetics and rare diseases research community. In particular, such support is essential in funding the clinical trials required to bring novel therapeutic approaches to

the clinic as therapies for previously untreatable disorders continue to be developed in the laboratory. These efforts are also essential for future progress because industry support is often lacking in rare disease treatment development because of the notion that there would be a limited financial return on such investments. This notion, however, has been contested by several authors who note that the treatment of IEM in particular may represent a niche market for some companies (24, 25). The NIH has also committed itself to the establishment and support of a strong clinical and translational research infrastructure within the biomedical community, evidenced by the implementation of the Clinical and Translational Science Award (CTSA) program, competitive awards that 24 institutions within the United States have received. The presence of such an infrastructure, from which researchers may draw basic laboratory, personnel, biostatistical, informatics and other support, may prove particularly useful in the search for new treatments in rare disorders.

Have we made progress in the last few years?

The establishment of the RDCRN represents a step forward, at least for the limited number of rare disorders included in the network, and the number of published clinical trials for rare genetic diseases has increased in the last several years. However, it remains to be seen just how quickly empiric data will be available for the majority of rare conditions. One thought-provoking suggestion has been the idea of requiring trainees in medical genetics to submit an evidence-based review, suitable for publication, as a capstone project on a rare genetic disease of their choice (16) as a requisite for board certification. This project would ideally complement the trainee's existing EBM training and bring together knowledge gleaned from both their clinical and biostatistical training.

The burden of proof?

Many rare genetic disorders are characterized by their relentless progression, prompting a sense of urgency on the part of the patient's family and treating physician. Extraordinary examples of efforts by parents, physicians, and researchers to initiate clinical treatment trials are well documented, particularly in the pediatric population (26–28). Often, in the past, little evidence was needed in order for a therapy to be utilized for rare genetic disorders and even approved by regulatory agencies such as the US FDA, likely because of what was perceived to be an urgent unmet clinical

need or because of the perception that well-designed RCTs could not be performed due to the disorder's rarity and/or a paucity of resources. In some cases, the urgency felt by researchers and treating physicians led to the expeditious introduction of effective therapies (29). In other cases, this sense of urgency may itself raise serious clinical and ethical concerns (30). The present-day corollary to this storied history is that many currently utilized therapies enjoy widespread acceptance despite little data supporting their effectiveness. Such is the case in the use of supplemental dietary cholesterol for Smith–Lemli–Opitz syndrome, which was shown not to affect cognitive outcomes in the largest study of its kind to date for that disorder (31), and the use of carnitine in medium chain acyl-CoA dehydrogenase deficiency (MCADD) (29). The introduction of such therapies into widespread use without conclusive evidence of efficacy can have the effect of painting advocates of EBM into a corner; ‘proper’ RCTs cannot ethically be designed when by definition the placebo group would have an unsubstantiated but nevertheless gold standard therapy for a life-threatening disease withheld.

What then to do with these accepted but unproven therapies? One solution may be to use these unproven standards to represent typical therapy. In so doing, a natural ‘standard of care’ control group will be available for trials comparing up-and-coming treatments with these established, albeit unproven, standards. This strategy may prove especially fair to parents and families. When faced with a progressive degenerative disease, it may be more appropriate to randomize patients between two treatment arms than it would be to include a true placebo group, particularly if the risk of a given treatment is low. Parents may then be more inclined to enroll their children and support ongoing research efforts if it will not keep them from receiving potentially valuable, if unproven, treatments. As an evidence base for rare disorders becomes increasingly established, this evidence may in turn be used to drive theories underlying relevant pathophysiology and further understanding of the condition as a whole.

The need for objective evaluation of burgeoning therapies

A number of new therapies have been developed for rare genetic diseases within the past decade or so. These advances include major strides forward in enzyme replacement therapy (ERT), spurred by the incentives put forth in the FDA's Orphan Drug Act of 1983; similar orphan drug legislation is also in place in many other countries. ERT is

currently approved for clinical use in the treatment of lysosomal storage disorders such as Fabry, Gaucher, and Pompe diseases and mucopolysaccharidosis types I, II and VI. In addition, efforts to produce other enzymes (i.e. beta-hexosaminidase A for Tay–Sachs and Sandhoff diseases) through ERT and other approaches are ongoing (32), with clinical trials planned for the future. Although results to date using ERT have been promising (33), data are still accumulating to determine the effect of these approaches on long-term outcome in lysosomal storage diseases that involve the central nervous system (CNS). In general, RCTs of ERT represent feasible goals, although collaboration between centers will likely be necessary to achieve appropriate statistical power, and more stringent evidence will need to be built upon prior, less rigorous studies, such as safety trials and cohort studies. For the present time, consensus-based standards derived from available evidence, such as the National Specialist Commissioning Advisory Group (NSCAG) guidelines for the treatment of lysosomal storage diseases (34) created by the UK Department of Health, help provide guidelines for the rational use of therapies such as ERT. Such guidelines, of course, are subject to all the limitations inherent in consensus-based algorithms.

In addition, ERT has thus far had a lesser effect on CNS manifestations (35) because the enzymes do not cross the blood–brain barrier (BBB) readily. Solutions to the BBB problem are in development and include the direct administration of therapeutic agents into the CNS through an intrathecal approach (36). A clinical trial of intracerebral injection of purified human fetal neural stem cells for infantile and late infantile neuronal ceroid lipofuscinosis (37) has also been initiated. Although much work remains to be done, innovative CNS targeting approaches continue to be developed and include the use of BBB-specific monoclonal antibody conjugates (38) as well as the possibility of using pharmacologic agents such as epinephrine (39) or higher risk but established techniques such as osmotic BBB disruption (40) to enhance CNS delivery. Furthermore, research aimed at enhancing cellular uptake by conjugation to delivery vehicles such as HIV Tat protein (41) or by use of glycosylation-independent chimeric proteins (42) is ongoing. All such therapies should be progressively evaluated for evidence of safety and efficacy as they are developed, progressing through the ranks of levels of evidence (Table 2). It remains a matter of clinical judgment on the part of the treating physician to determine when the potential benefit outweighs the risk involved in administering a given treatment. The

risk of non-treatment is great in many rare disorders but may be minimal in others (not all patients with rare disorders require improved treatment, as evidenced by the widely publicized Jesse Gelsinger case where a young man with a stable rare disorder died while participating in a clinical trial). It is expected that practice parameters and similar evidence summaries will be of great use in continuing to evaluate new therapies as they develop.

In addition, other novel interventions for rare genetic disorders continue to be developed and show promise. These therapies include the recent demonstration that a pharmacologic ‘read-through’ molecule (PTC124) can be used to produce full-length peptides from mutant templates that would otherwise lead to premature truncation codons (43). This therapy would thus have potential application in any disorder characterized by a nonsense mutation, leading to loss of function of the resultant protein product. Clinical trials using PTC124 as a treatment for Duchenne muscular dystrophy (44) and cystic fibrosis (45) characterized by nonsense mutations are underway, and preliminary data have been encouraging (46). Trials of this nature should ultimately progress to RCTs evaluating specific treatments in the disorders of interest.

Chaperone therapies aimed at pharmacologically ‘correcting’ a misfolded protein product are also being developed (47–49), and clinical trials using these compounds are underway (50). Potential benefits of this therapeutic approach include the fact that therapeutic chaperones represent small molecule agents that may circumvent the problems of CNS penetration and intracellular delivery that plague other approaches. However, despite the hope these examples hold for the future development of effective therapeutics, most efforts remain in pre-clinical trials.

With several limitations already identified that affect the rare disease community’s ability to produce high-quality studies, it is likely that a variety of studies of various quality will be needed to be analyzed and integrated to produce useful guidelines to guide clinical practice. This ability to synthesize studies and thereby bring research findings into the clinic will be key in efforts to move ahead.

Applying available EBM

In the effort to apply the best available evidence, what resources are available to identify the relevant literature? Once the appropriate literature is at hand, what criteria should then be used to evaluate these studies?

What standards should be utilized for rare disorders?

The ‘gold standard’ of EBM is the prospective, randomized, double-blind, placebo-controlled trial. Such a design is the least biased (51) (Table 2). As such, it represents a laudable ideal. However, when applied to rare genetic disorders, such a construct is often just that: an ideal. For many of the reasons discussed above, including the limited number of subjects available for enrollment (limiting the study’s power), difficulty in securing rigorously matched groups because of age-related variation, phenotypic heterogeneity, and the ethical considerations involved in withholding potentially life-altering treatment from a placebo-bound control group, it may be difficult and many times practically impossible to apply such a rigorous standard. This classic mismatch between study conceptualization and clinical implementation with real patients is thus magnified in the fields of medical genetics and rare disorders. Many of these issues are eloquently discussed in publications by Lilford et al. (52), Wilcken (53), and Kohlschuetter (54) and led Wilcken to suggest a somewhat relaxed hierarchical stratification of available EBM in rare disorders. The underlying principle was that the opportunity to perform clinical trials in rare disorders should not be passed up if a less-than-ideal study is the only one able to be performed, that limited data is better than no data and that case series or even case reports still retain scientific value as they come into being by hard-fought clinical battles. Accommodations may be necessary when applying EBM to rare disorders, but the moniker ‘best available evidence’ should not be forgotten. Financial resources will also limit the rare disease community’s ability to generate rigorous evidence-based standards, and ultimately the complex interplay between patients, their families, researchers, clinicians, and policy makers will determine what is possible. Figure 1 presents one conceptual integration of levels of evidence as applied to rare disorders.

Identifying the ‘best available’ evidence

So, how does one go about searching for relevant EBM in rare genetic disorders? The typical place to start is with PubMed where keywords are applied and a wide net is cast to capture the appropriate searches. Keywords are derived from the searchable content of an individual abstract as well as the medical subject heading (MeSH) terms that are suggested by the article’s authors and the journal’s editors but ultimately chosen by PubMed indexers. To some extent, PubMed sacrifices

A three-tiered approach to improving the application of EBM to rare genetic disorders

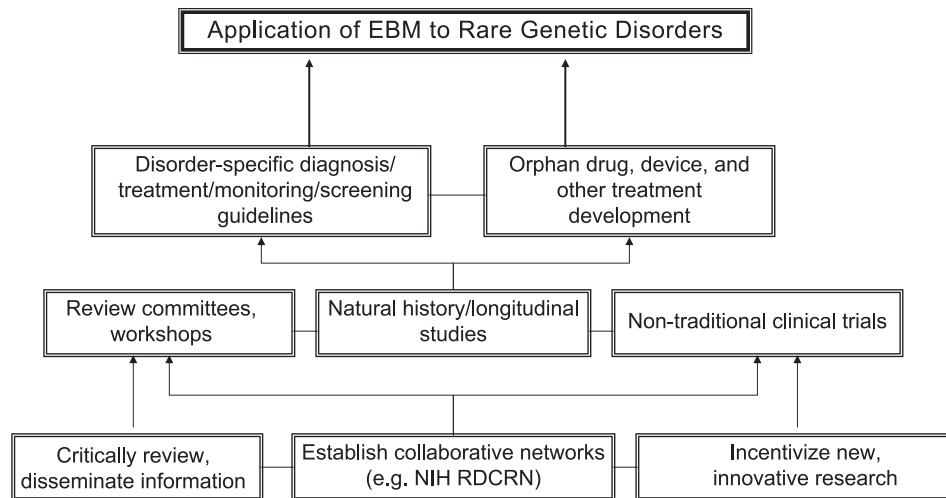


Fig. 1. A three-tiered approach to increase the application of evidence-based medicine (EBM) to rare genetic disorders is depicted. Each tier is built upon a foundation that in turn supports the next level. Interrelationships between tiers are integral to this model.

specificity for sensitivity and relies on the ‘Related Articles’ feature to connect users to relevant works. User-friendly aspects of PubMed include the ability to save searches or to limit searches to exclude non-relevant terms that would otherwise appear with high frequency. The ‘Clinical Queries’ subsection features a ‘Medical Genetics Searches’ feature that may be used to optimize yield. Furthermore, under the ‘Limits’ tab on the PubMed homepage is the ability to limit searches to ‘Clinical Trials’ or ‘Randomized Controlled Trials’.

Despite all the powerful capabilities of PubMed, prior publications have identified limitations of the engine’s search algorithms (16). After all, in-

dexers can only list a small number of MeSH terms under which to group an individual article. The system’s algorithm is reliant on proper indexing and abstract content to capture a salient work for the intended audience. Prior authors have reported that despite all of PubMed’s features and abilities, hand searching of relevant topic material (i.e. personally scanning the references section of relevant articles and manually retrieving potentially important ones) is still necessary because PubMed inevitably misses important articles (55). Many systematic reviews and meta-analyses thus still include hand searching of relevant abstracts among their search strategies.

Table 4. Special considerations in applying EBM to rare genetic disorders: many challenges, some answers

Uncommon aspects of rare disorders

Few patients are affected by rare disorders; too few for single center clinical trials

Collaborative, multi-site RCTs

Difficult to perform randomized placebo-controlled trials for accepted but unproven therapies in fatal disorders

Compare novel therapies to ‘gold standard’ accepted (but often unproven) therapies instead of placebo

Inherent limitations in the application of EBM

Population-based averages may not be applicable to individual patients

Heterogeneity of diseases may limit applicability; may be offset by stringent attempts to control confounding variables, perhaps using multi-site RCTs

Based on empiricism; does not take theory into account

Collected evidence may be useful in shaping theory

Narrow definition of evidence

Need to broaden types of evidence considered. The $n = 1$ crossover trial, case report, case series, and natural history study may all contain useful information that can be considered as part of a weighted evidence base

Potential threat to physician autonomy

Evidence-based support for subspecialists who often practice outside of most physicians’ comfort zone

EBM, evidence-based medicine; RCT, randomized clinical trial.

Biomedical informatics, the field dedicated to using computational methods to organize and analyze biomedical data, is thriving. Established methods exist to scan the genome, transcriptome, and proteome for meaningful data and establish relationships among complex and dynamic variables. So, the question must be asked: in this era of boom in biomedical informatics, how is it that we are able to scan the entire genome to find a single upregulated gene among tens of thousands when interpreting microarray data but we seem unable to retrieve the best articles to guide us in treating otitis media? Is hand searching really necessary?

Several additional, web-based resources are available, created to address this very issue, including search engines that are widely accessible to the general public, such as Google Scholar (56). Although an exhaustive evaluation of the strengths and weaknesses of each approach is outside the scope of this review, the interested reader is directed to MetaDB (57), which serves as a repository for such bioinformatic tools. It should be evident from the sheer number of such tools that exist that no search algorithm is perfect. The available interfaces have distinct objectives, with varying sensitivity and specificity to be expected based on each algorithm's particular focus. Relevant articles will inevitably be missed. Conversely, depending on the degree to which the reader tries to be inclusive, increasing numbers of non-relevant articles that nevertheless feature key terms specified will be included. Hand searching may not be necessary, but the search engine-driven researcher will be forced to utilize a number of search engines to be inclusive or at least to wade through the irrelevant hits derived from a single source. In the current era, then, despite the difficulty in defining any single search strategy as 'all-inclusive', finding relevant literature to guide clinical decision-making is eminently achievable.

Once the 'best available' evidence has been culled, it needs to be systematically evaluated, summarized, and contextualized. Although also outside the scope of this review, a number of excellent works detailing this process exist (58, 59), and the exact criteria for evaluating the strength of existing evidence vary from professional organization to organization. The Cochrane Collection, in its systematic searches, attempts to gather both published and unpublished evidence on a topic, recognizing the bias toward demonstrating differences that journals typically seek when evaluating works for their 'publishability'.

The Cochrane Library's Cystic Fibrosis and Genetic Disorders Working Group, in particular, is committed to expanding the number and scope of systematic reviews available regarding diagnosis and treatment of rare genetic diseases (60). The

vast majority of currently available reviews focus on various aspects of cystic fibrosis and other 'high-profile' genetic disorders, such as sickle cell anemia, thalassemia and the hemophilias, and phenylketonuria. However, more recently, reviews have been initiated on topics such as enzyme replacement therapy in Fabry disease, carnitine supplementation in IEM, and the use of bone marrow transplantation in Gaucher disease. In addition, a systematic review of the pharmacologic treatment of osteogenesis imperfecta has recently been completed (61). In addition to the systematic reviews provided by the Cochrane Library, several expert panels have published guidelines for diagnosis and management of various IEM (62, 63). These guidelines are an amalgamation of published evidence and expert consensus and should be useful in application of the best available evidence for the systematic management of these complex patients. Finally, the US Centers for Disease Control and Prevention (CDC) has established a collaborative task force, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP; 64), that is beginning to systematically review the evidence base for commercially available genetic and genomic tests that may soon be applied to the diagnosis of rare disorders.

When available evidence is scant to non-existent, particularly in the case of extremely rare or newly recognized disorders, expert opinion derived from experience may represent the best available evidence. In such cases, modern day global connectivity, through e-mail, telephone, and the World Wide Web, may serve as our best search engine. In particular, as was recently proposed by Kohlshuetter (54), foundations may serve vital roles not only as patient support networks and catalysts for research but also help practitioners access experts in consultation on difficult cases. The National Organization for Rare Disorders (65) serves as one such model in efforts to bring together patients, clinicians, and researchers with a shared focus on improving both diagnostics and available therapies.

Conclusions

In summary, EBM can be extremely helpful in guiding evaluation and treatment, although the ultimate responsibility for the medical care of the patient with a rare genetic disease remains with the treating physician. The very nature of 'rare genetic diseases' challenges the generation and application of relevant data regarding their screening, diagnosis, management, and monitoring. However, although RCTs in rare diseases will continue to be difficult to produce, this should be the

ultimate goal of researchers in the field, and progress should continue to be made through natural history studies and smaller, alternative trial designs that nevertheless can provide useful data to guide management and spur future research.

The establishment of a collaborative, multi-institutional research infrastructure has perhaps begun with the development of the RDCRN and similar rare disease networks. Although there is currently a US NIH funding 'drought' and a similar dearth of research funding in other countries, the mechanisms to fund important rare disease research have been established and build upon the earlier efforts of foundations and non-profit initiatives. As new and innovative approaches continue to be developed and brought to the clinical trial level, this network should continue to expand and develop in response to the needs of the rare disease community. In particular, collaborations between academic institutions and industry will be key, and more innovative funding programs, perhaps built upon a model such as the NIH Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs (66), are needed. This type of public-private partnership may be important in bringing orphan treatments to market. Furthermore, established research networks may play a key role not only in generating evidence-based results but also in disseminating these results to practitioners through meta-analyses, practice parameters, and topic summaries.

Rare disorders magnify the strengths and limitations of EBM. Despite concerns that EBM may threaten physicians' autonomy, establishment of an evidence base may in fact lend credence to beneficial current practices, lead physicians to abandon inadequate or dangerous therapies, and generally guide clinicians in areas of uncertainty. There is inherent difficulty in applying 'the average' scenario to heterogeneous disorders, but efforts to collaborate to increase sample size and produce the most stringent studies possible may represent a potential solution. Finally, the difficult integration of current best evidence and contemporary theory may simultaneously help to guide clinical management and spur new areas of investigation in rare disorders.

Although limitations exist, a number of excellent databases exist for identifying EBM, with PubMed continuing to occupy a central niche. Furthermore, the methods and terminology used in curated databases are constantly undergoing a process of review and critique. As such, indexing is a dynamic process that tries to conform itself to meet users' needs. As biomedical research in rare genetic disorders continues to evolve, so too will

the ability to access the available literature in a busy clinical setting.

Ultimately, in order for the field to continue to progress, medical geneticists and other clinicians caring for patients with rare diseases as well as researchers need to capitalize upon the opportunity afforded by the development of collaborative networks. There needs to be a commitment to not only provide the best available treatment to individual patients but also to share these experiences with the community at large and to publish both unorthodox study designs (i.e. the $n = 1$ crossover design) and provocative case series as well as more rigorous investigations. With more prolific reports comes both the ability to integrate more diverse sources of evidence into a cohesive whole (67) and the need to more frequently evaluate the available literature. This may be accomplished by enlisting the help of trainees, establishing consensus panels, ideally through collaborative, disease-centered networks, and/or by providing grant support to convene expert panels, as has been done for more common disorders such as cerebral palsy (68). The development of an integrated national or international system by which collaborative research in rare genetic disorders is supported should be a top priority. This will enable the creation of both needed biorepositories and registries of affected patients, as recently called for by a national collaborative panel (69). Study validity and applicability may be improved by supporting research on innovative trial design, and granting agency study sections may benefit from ensuring that specialists expert in the rare disease under review are included. The literature needs to be continuously evaluated, evidence-based standards need to be established when possible, and areas for further research identified. Clinical and research symposia, organized around the application of the best available evidence for screening, diagnosis, management, and monitoring of rare disorders, should be organized to provide clinicians and researchers a forum in which to meet and exchange ideas. In this way, we may continue to move ahead the research agenda for both individual disorders and the field of rare genetic disorders as a whole.

Acknowledgements/Disclosures

M. C. K. receives support through the Oregon Clinical and Translational Research Institute (OCTRI), grant number UL1 RR024140 from the NCCR, a component of the NIH, and NIH Roadmap for Medical Research.

R. D. S. receives research grant support from the NIH and private foundations and has received research support and honoraria for lectures from biopharmaceutical companies. He is the principal investigator of an industry-sponsored clinical trial on the safety

and preliminary efficacy of fetal neural stem cells in the treatment of infantile and late infantile neuronal ceroid lipofuscinosis.

References

1. Haynes RB. What kind of evidence is it that Evidence-Based Medicine advocates want health care providers and consumers to pay attention to? *BMC Health Serv Res* 2002; 2 (1): 3.
2. Rubenstein JH, Inadomi JM. Evidence based medicine (EBM) in practice: applying results of cost-effectiveness analyses. *Am J Gastroenterol* 2006; 101 (6): 1169–1171.
3. Charlton BG, Miles A. The rise and fall of EBM. *QJM* 1998; 91 (5): 371–374.
4. Harari E. Whose evidence? Lessons from the philosophy of science and the epistemology of medicine. *Aust N Z J Psychiatry* 2001; 35 (6): 724–730.
5. Bleck TP. Alternatives to evidence-based medicine. Different rating scale could be used. *BMJ* 2000; 321: 239.
6. Cohen AM, Stavri PZ, Hersh WR. A categorization and analysis of the criticisms of evidence-based medicine. *Int J Med Inform* 2004; 73 (1): 35–43.
7. Anonymous. Evidence-based medicine, in its place. *Lancet* 1995; 340: 1131–1132.
8. Hill GB. Archie Cochrane and his legacy. An internal challenge to physician's autonomy? *J Clin Epidemiol* 2000; 53: 1189–1192.
9. Smith GC, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. *BMJ* 2003; 327 (7429): 1459–1461.
10. Sox H. Screening mammography for younger women: back to basics. *Ann Intern Med* 2002; 137 (5 Pt 1): 361–362.
11. Naylor CD. Clinical decisions: from art to science and back again. *Lancet* 2001; 358 (9281): 523–524.
12. Retrieved March 30, 2008, from www.cochrane.org.
13. Dorsch JL, Aiyer MK, Meyer LE. Impact of an evidence-based medicine curriculum on medical students' attitudes and skills. *J Med Libr Assoc* 2004; 92 (4): 397–406.
14. Flores-Mateo G, Argimon JM. Evidence based practice education in postgraduate health care: a systematic review. *BMC Health Serv Res* 2007; 7 (1): 119.
15. Evans J, Khoury MJ. Evidence based medicine meets genomic medicine. *Genet Med* 2007; 9 (12): 799–800.
16. Steiner RD. Evidence based medicine in inborn errors of metabolism: is there any and how to find it. *Am J Med Genet A* 2005; 134 (2): 192–197.
17. Hunter AG. Is multicenter collaborative research in clinical genetics dead and, if so, what killed it? *Am J Med Genet A* 2005; 134 (3): 237–239.
18. Stacpoole PW, Kerr DS, Barnes C et al. Controlled clinical trial of dichloroacetate for treatment of congenital lactic acidosis in children. *Pediatrics* 2006; 117 (5): 1519–1531.
19. Retrieved March 30, 2008, from <http://rarediseasesnetwork.epi.usf.edu/>.
20. Retrieved March 30, 2008, from <http://www.mrc.ac.uk/ApplyingforaGrant/CallsForProposals/ClosedCalls/Cohorts/Initiative/index.htm>.
21. Retrieved March 30, 2008, from <https://www.portcf.org/>.
22. Goss CH, Mayer-Hamblett N, Kronmal RA, Ramsey BW. The cystic fibrosis therapeutics development network (CF TDN): a paradigm of a clinical trials network for genetic and orphan diseases. *Adv Drug Deliv Rev* 2002; 54 (11): 1505–1528.
23. Retrieved March 30, 2008, from <http://www.cettprogram.org/>.
24. Werber Y. Lysosomal storage diseases market. *Nat Rev Drug Discov* 2004; 3 (1): 9–10.
25. Wraith JE. Limitations of enzyme replacement therapy: current and future. *J Inherit Metab Dis* 2006; 29 (2–3): 442–447.
26. Odone A, Odone M. More on Lorenzo's oil. *N Engl J Med* 1994; 330 (26): 1904–1905.
27. Moser HW, Raymond GV, Lu SE. Follow-up of 89 asymptomatic patients with adrenoleukodystrophy treated with Lorenzo's oil. *Arch Neurol* 2005; 62 (7): 1073–1080.
28. Rizzo WB, Leshner RT, Odone A. Dietary erucic acid therapy for X-linked adrenoleukodystrophy. *Neurology* 1989; 39 (11): 1415–1422.
29. Walter J. L-carnitine in inborn errors of metabolism: what is the evidence? *J Inherit Metab Dis* 2003; 26: 181–188.
30. Peters C, Krivit W. Hematopoietic cell transplantation for mucopolysaccharidosis IIB (Hunter syndrome). *Bone Marrow Transplant* 2000; 25 (10): 1097–1099.
31. Sikora DM, Ruggiero M, Petit-Kekel K et al. Cholesterol supplementation does not improve developmental progress in Smith-Lemli-Opitz syndrome. *J Pediatr* 2004; 144 (6): 783–791.
32. Akeboshi H, Chiba Y, Kasahara Y et al. Production of recombinant beta-hexosaminidase A, a potential enzyme for replacement therapy for Tay-Sachs and Sandhoff diseases, in the methylotrophic yeast *Ogataea minuta*. *Appl Environ Microbiol* 2007; 73 (15): 4805–4812.
33. Wraith JE, Beck M, Lane R et al. Enzyme replacement therapy in patients who have mucopolysaccharidosis I and are younger than 5 years: results of a multinational study of recombinant human alpha-L-iduronidase (laronidase). *Pediatrics* 2007; 120 (1): e37–e46.
34. Retrieved April 18, 2008, from http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4118406.
35. Beck M. New therapeutic options for lysosomal storage disorders: enzyme replacement, small molecules and gene therapy. *Hum Genet* 2007; 121 (1): 1–22.
36. Dickson P, McEntee M, Vogler C et al. Intrathecal enzyme replacement therapy: successful treatment of brain disease via the cerebrospinal fluid. *Mol Genet Metab* 2007; 91 (1): 61–68.
37. Retrieved March 30, 2008, from <http://www.clinicaltrials.gov/ct2/show/NCT00337636>.
38. Zhang Y, Pardridge WM. Delivery of beta-galactosidase to mouse brain via the blood-brain barrier transferrin receptor. *J Pharmacol Exp Ther* 2005; 313 (3): 1075–1081.
39. Urayama A, Grubb JH, Banks WA, Sly WS. Epinephrine enhances lysosomal enzyme delivery across the blood brain barrier by up-regulation of the mannose 6-phosphate receptor. *Proc Natl Acad Sci U S A* 2007; 104 (31): 12873–12878.
40. Neuwelt EA, Barranger JA, Brady RO et al. Delivery of hexosaminidase A to the cerebrum after osmotic modification of the blood-brain barrier. *Proc Natl Acad Sci U S A* 1981; 78 (9): 5838–5841.
41. Lee KO, Luu N, Kaneski CR et al. Improved intracellular delivery of glucocerebrosidase mediated by the HIV-1 TAT protein transduction domain. *Biochem Biophys Res Commun* 2005; 337 (2): 701–707.
42. LeBowitz JH, Grubb JH, Maga JA. Glycosylation-independent targeting enhances enzyme delivery to lysosomes and decreases storage in mucopolysaccharidosis type VII mice. *Proc Natl Acad Sci U S A* 2004; 101 (9): 3083–3088.
43. Welch EM, Barton ER, Zhuo J et al. PTC124 targets genetic disorders caused by nonsense mutations. *Nature* 2007; 447 (7140): 87–91.
44. Wilton S. PTC124, nonsense mutations and Duchenne muscular dystrophy. *Neuromuscul Disord* 2007; 17 (9–10): 719–720.
45. Zeitlin PL. Emerging drug treatments for cystic fibrosis. *Expert Opin Emerg Drugs* 2007; 12 (2): 329–336.

46. Wong B, Bonnemann C, Finkel R et al. Phase 2 study of PTC124 for nonsense mutation suppression therapy of Duchenne muscular dystrophy (DMD). Platform presentation 2007: 36th Annual Child Neurology Society Meeting, Quebec, Canada. *Ann Neurol* 2007; 62: S11–S96.
47. Zheng W, Padia J, Urban DJ et al. Three classes of glucocerebrosidase inhibitors identified by quantitative high-throughput screening are chaperone leads for Gaucher disease. *Proc Natl Acad Sci U S A* 2007; 104 (32): 13192–13197.
48. Shin SH, Murray GJ, Kluepfel-Stahl S et al. Screening for pharmacological chaperones in Fabry disease. *Biochem Biophys Res Commun* 2007; 359 (1): 168–173.
49. Okumiya T, Kroos MA, Vliet LV et al. Chemical chaperones improve transport and enhance stability of mutant alpha-glucosidases in glycogen storage disease type II. *Mol Genet Metab* 2007; 90 (1): 49–57.
50. Retrieved March 30, 2008, from <http://clinicaltrials.gov/ct/show/NCT00446550>.
51. Lachin JM, Matts JP, Wei LJ. Randomization in clinical trials: conclusions and recommendations. *Control Clin Trials* 1988; 9 (4): 365–374.
52. Lilford RJ, Thornton JG, Braunholtz D. Clinical trials and rare diseases: a way out of a conundrum. *BMJ* 1995; 311 (7020): 1621–1625.
53. Wilcken B. Rare diseases and the assessment of intervention: what sorts of clinical trials can we use? *J Inherit Metab Dis* 2001; 24 (2): 291–298.
54. Kohlschuetter A. Mastering the dilemma of rare diseases. *Neuropediatrics* 2007; 38: 1.
55. Poustie V, Rutherford P. Dietary interventions for phenylketonuria. *Cochrane Database Syst Rev* 2000: CD001304.
56. Retrieved March 30, 2008, from <http://scholar.google.com/schhp?hl=en&tab=ws>.
57. Retrieved March 30, 2008, from www.neurotransmitter.net/metadb/index.php?catid=65.
58. Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB. *Evidence-Based Medicine: How to Practice and Teach EBM*, 3rd edn. Edinburgh: Churchill Livingstone, 2000.
59. Straus SE, Richardson WS, Glasziou P, Haynes RB. *Evidence Based Medicine*, 3rd edn. Edinburgh: Churchill Livingstone, 2005.
60. Retrieved March 30, 2008, from www.cochrane.org/reviews/en/topics/55.html.
61. Steiner RD, Reeder J. Pharmacologic treatment for improving bone density in people with osteogenesis imperfecta. *Cochrane Database Syst Rev* 2005, Issue 1. Art. No.: CD005088. DOI: 10.1002/14651858.CD005088
62. Kishnani PS, Steiner RD, Bali D et al. Pompe disease diagnosis and management guideline. *Genet Med* 2006; 8 (5): 267–288.
63. Kölker S, Christensen E, Leonard JV et al. Guideline for the diagnosis and management of glutaryl-CoA dehydrogenase deficiency (glutaric aciduria type I). *J Inherit Metab Dis* 2007; 30 (1): 5–22.
64. Retrieved March 30, 2008, from www.egapreviews.org.
65. Retrieved March 30, 2008, from <http://www.rarediseases.org>.
66. Retrieved March 30, 2008, from www.grants.nih.gov/grants/funding/sbirsbttr_program.htm.
67. Khoury MJ, Gwinn M, Burke W, Bowen S, Zimmern R. Will genomics widen or help heal the schism between medicine and public health? *Am J Prev Med* 2007; 33 (4): 310–317.
68. Rosenbaum P, Paneth N, Leviton A et al. A report: the definition and classification of cerebral palsy April 2006. *Dev Med Child Neurol Suppl* 2007; 109: 8–14.
69. Watson MS, Epstein C, Howell RR, Jones MC, Korf BR, McCabe ER, Simpson JL. Developing a national collaborative study system for rare genetic diseases. *Genet Med* 2008; 10 (5): 325–329.

Copyright of *Clinical Genetics* is the property of Blackwell Publishing Limited and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.