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Editorial

Moving from research to practice: relevance and generalizability

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Epidemiology is occurrence research.[1] The object of epidemiologic research is the occurrence of illness and its relation to determinants (occurrence relation). Similar to other epidemiologic research, the motive for applied clinical studies is to learn about an object. Eventually, the knowledge produced by the research needs to be incorporated in the knowledge base that guides daily medical care. During the design and conduct of research, it is important to keep this aim in mind and be aware of the effects that choices in the design of the study may have on the applicability and implementation of the results.

In the critical theoretical, initial phase of study design, the occurrence relation is laid out with all of its elements. Following the theoretical design, a plan is made of how to obtain and summarize knowledge on the nature and strength of the occurrence relation from available or induced experience, e.g., from empirical data collected in groups of subjects. Here, a number of decisions need to be taken, apart from the actual way data are being collected. To be able to move from theoretical design to data collection, the occurrence relation needs to re-phrased in both theoretical and operational terms. This will not only point the way to measurement techniques in data collection but also indicate compromises that need to be made to match the ideal format of information on outcome and determinants to what can practically be achieved. For example, suppose we wish to precisely quantify the relation between presence of heart failure and subsequent loss of patient autonomy and quality of life. In the data collection, we may then have to settle for dyspnea to classify heart failure and the Euroqol questionnaire to assess quality of life.[2] This need not be a problem, but it is important that these choices are made explicit and recognized in the interpretation of the research. Both the measure of the outcome and the determinant are mere proxies for what we really aim to evaluate. In applied clinical research, it is commonly important to stay close to what matters to patients when deciding upon measures of outcome of diseases. This is not necessarily intuitive to all clinical investigators.

Not infrequently, investigators rely most on what can be quantified in solid measures rather than on what has the biggest impact for a patient. We reviewed studies on new positive inotropic drugs in heart failure.[3] The profound impact that congestive heart failure has on life expectancy and quality of life has been a continuous stimulus for the development of

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new drugs for the treatment of this condition. Despite favorable effects on (aspects of) quality of life in short-term studies, several new agents have been shown to reduce survival in mortality trials. However, patients with severe congestive heart failure may experience such incapacitating symptoms that the question should be raised as to whether an improvement in quality of life makes the increased risk of mortality associated with these new agents acceptable. Drugs that improve quality of life at the expense of an increased risk of mortality can be of value in the treatment of patients with severe congestive heart failure. However, this is only the case if the probability of improvement in quality of life and prolongation of life expectancy for those using the drug exceeds the probability of improvement in quality of life and prolongation of life expectancy for those not using the drug. Unfortunately, most clinical trials in which both mortality and quality of life are evaluated fail to provide information on this composite probability. In clinical research there is a justified growing emphasis on measures of disease that matter to patients, the importance of which was underlined by the outcomes movement and summarized in a seminal publication in the New England Journal of Medicine in 1988.[4]

Questions that trigger applied clinical research result from problems and lack of knowledge perceived in patient care. Certain questions are relevant for certain groups of patients and not to others. Consequently, research findings may be relevant to smaller or larger groups of patients. The essence of scientific research, in contrast to other forms of systematic gathering of data, is that its results can be generalized. The type of knowledge provided by clinical epidemiologic research is inferential, probabilistic knowledge. This knowledge contrasts with factual knowledge because it is not time- and place-specific. It is true for any patient or groups of patients as long as the findings, on which the knowledge is based, permit scientific generalization to those patients. The patient is a special case of a category of patients to whom the occurrence relation applies. In the initial theoretical phase of study design, a careful appreciation of the type of patients for which the research needs to be relevant is important. The (theoretical) population of patients to which the findings apply is called the *domain* of the study. The domain description can be viewed as a pharmaceutical package insert of a study: "please use for this type of patient". In the choice of a population for empirical data collection (= the study population), the domain should be kept in mind.

Members of the study population should represent the (virtual) population of the domain. Apart from criteria for selection of a study population that follow from the chosen domain, such as the severity of disease or a certain indication for diagnostic work-up, other restrictions may be necessary in recruiting participants in a study that result from logistic or other circumstances. Many of these additional restrictions, such as the need to live close to the research center and availability of time for additional diagnostic assessments, will not have an impact on the eventual applicability of the results and therefore will not in turn limit the domain. It is important to appreciate which characteristics of a study population are determined with a view to the intended domain and as such form part of the design, and which characteristics result from reasons beyond the theoretical design.

With a view to the study domain, those characteristics of the study population need particular consideration that bear on the generalizability of the empirical relation. The *generalizability* of research results, sometimes referred to as the *external validity* is the extent to which knowledge obtained in a particular type of patient may be generalized to another larger, theoretical, abstract group of patients. Suppose that a study is conducted to determine the value of a certain novel type of surgery in patients with a particular gastrointestinal disease. The results of the study could be that recovery in operated patients of type T is more common than in non-operated ones, conditional on all extraneous determinants (confounders) of recovery. The conclusion is that operation enhances recovery in patients of type T, without reference to time or place. The results are generalized from the group of patients in which the empirical data were collected to a larger group of theoretical patients representing the domain of the research.

Generalizability is not an objective process that can easily be framed in statistical terms. Moving from time- and place-specific findings to scientific knowledge requires judgement about the potential of other characteristics inherent to the research setting and study population to modify the nature and strength of the relation between determinant(s) and outcomes as estimated in the study.

Appreciation of generalizability is essential for scientific inference. Definition of the domain of a study as part of the occurrence relation is important because the domain of a relation provides the basis

> The essence of knowledge is generalization. That fire can be produced by rubbing wood a certain way is a knowledge derived from individual experiences; the statement means that rubbing wood in this way will always produce fire. The art of discovery is therefore the art of generalization. What is irrelevant, such as the particular shape or size of the piece of wood used is to be excluded from the generalization: what is relevant, for example, the dryness of the wood, is to be included in it. The meaning of the term relevant can thus be defined: that is relevant which must be mentioned for the generalization to be valid. The separation of relevant from irrelevant factors is the beginning of knowledge.

Reichenbach H in: The rise of scientific philosophy. New York: Harper and Row. 1965 (Quoted in Rothman, Modern Epidemiology)[5]

for generalization. As a rule, the utility of research is greater if the domain of the research findings, e.g., the generalizability of the estimated relations between outcome and determinants, is broader. Consequently, while the design of the occurrence relation needs to be precise and comprehensive, the domain is generally implicitly or explicitly kept broad. In diagnostic research, the domain is defined by the loosely defined patient profile representing those subjects for which a particular diagnostic question is relevant. In etiologic research the domain is formed by people at risk for the illness at issue and with variability of the causal factor at issue. For example, the domain for research on the etiological role of smoking in lung cancer are all human beings with lungs and the possibility to smoke. In prognostic research, again, the domain is defined by the patient profile of those for whom prognostic statements based on the determinants included in the research are considered. In research into effects of treatments the domain is those who may need treatment.

Where most elements of scientific research require maximal specificity, the domain is, in general, loosely defined. Apart from smaller or larger restrictions in the empirical data of a study, either by design or by circumstances, differences will persist to exist among those using the results of research with respect to their willingness to generalize to larger groups. For example, in the absence of results from randomized trials specifically demonstrating the clinical benefits of use of statins in women with elevated cholesterol levels, some people did not accept an indication for use of these drugs in women in spite of ample evidence of reductions of risk in men with similar risk profiles.

As a final point, it has increasingly been acknowledged that the principles and methods of epidemiology may be fruitfully employed in applied clinical research. In parallel with a growing emphasis in medicine to use quantitative evidence to guide patient care and to judge its performance, epidemiology has become one of the fundamental disciplines for patient-oriented research and a cornerstone for evidence-based medicine. To serve clinical practice best, research should be relevant, valid, and precise. Consequently, research results can eventually be applied with confidence in daily practice.

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