Benefits and limitations of laboratory diagnostic pathways

Abstract: Diagnostic pathways are an essential subset of clinical pathways and a logical consequence of DRG-based reimbursement. They combine the principle of stepwise reflex and reflective testing with a management concept that helps to fulfill medical needs with organizational and economic efficacy. The two most common formats describing diagnostic pathways are graphical decision trees on paper and “if…then…else” rules on computers. From a laboratory point of view, diagnostic pathways represent “smart” test profiles, which – in contrast to conventional (inflexible) profiles – are not necessarily worked off completely, but just to a point, where a diagnostic decision can be made. This improves the cost-effectiveness of laboratory testing, while making sure that no essential tests are missed. The paper describes benefits and limitations of diagnostic pathways from a medical, organizational, and economic point of view. Their major advantage is also their major drawback, since they make the diagnostic process on the one hand extremely straight-forward and transparent, while on the other hand oversimplifying the underlying medical decision principles. This may provoke the abuse of their primarily medical intentions for mere economic purposes.

Keywords: AWMF; clinical pathways; diagnosis-related groups; directives; guidelines; laboratory diagnostic pathways; laboratory management; profiles; recommendations.

Introduction

Around the year 2000, several hospitals in Germany and other European countries started to use industrial management strategies, in order to improve their competitiveness in times of increasing cost pressure. Originally, these models and methods had been developed in Anglo-Saxon countries, where “clinical pathways” for optimization and control of clinical business processes have been in use since the 1990s [1]. The lagged introduction in Germany was at least in part due to the fact that in this country diagnosis-related groups (DRGs) were introduced with a delay of decades as compared to the United States, Canada, UK, or Australia [2].

Clinical pathways have been established in practically all countries with DRG-based reimbursement systems. They represent a crucial ingredient of clinical workflow management systems (WMF) [3] and are a more or less logical consequence of the fact that fixed prices require standardized processes; otherwise costs tend to get out of control. This is especially true for diagnostic processes, since they represent the very beginning of most hospital stays. Errors made at the start may entail many consecutive mistakes, and wrong diagnoses may lead to insufficient therapies. Although these remarks may seem self-evident, “diagnostic pathways” attracted much less attention in the past than clinical “care pathways”, probably because treatment is more expensive than diagnostics.
In order to put more emphasis on diagnostic issues in the context of clinical pathways, the German Association for Clinical Chemistry and Laboratory Medicine DGKL (www.dgkl.de) started an initiative in 2006, aiming to define the specific rules for the implementation of laboratory diagnostic pathways as a subset of clinical pathways. This activity led to the publication of a handbook for laboratory diagnostic pathways in 2012, which recently appeared in its second edition [4]. It includes more than 80 graphs, presenting pathway examples for various medical fields, such as metabolism, hematology, and immunology, to name just a few. In 2012, laboratory representatives of the German-speaking countries Austria, Switzerland and Liechtenstein joined this initiative. To our knowledge, this is the first international group dedicated especially to laboratory diagnostics pathways. A comparable initiative exists in Australia for diagnostic imaging pathways (www.health-direct.gov.au/partners/diagnostic-imaging-pathways).

Definitions

A laboratory diagnostic pathway describes the entire process from the initial medical question to the final result [4]. It encompasses the right tests for defined questions (WHAT) with a professional reasoning (WHY) and – if necessary – with a time label (WHEN). In contrast to clinical pathways, where the correct timing of all actions needs to be guaranteed by humans, laboratory tests (biomarkers) can often be sequentially analyzed without human interaction, just using information technology and analytical automation systems. Exceptions are follow-up tests (e.g. drug monitoring) or certain cases, where an unexpected laboratory result needs a confirmation test or additional sample material.

Diagnostic pathways combine the well-known principle of stepwise reflex and reflective testing [5] with a management concept that helps to fulfill medical needs with organizational and economic efficacy [6]. In essence, diagnostic pathways are “smart” test profiles, which – in contrast to conventional inflexible laboratory profiles – are not necessarily worked off completely, but just to a point, where the diagnostic decision can be made. Formally, such pathways may be represented either in a rule-format (if... then... else...) or by graphical decision trees (so-called “algorithms”). Diagnostic pathways play an essential role in the beginning of diagnostics, notably to rule out frequent causes of acute and chronic syndromes such as diabetes mellitus (Figure 1). They usually follow

![Diagram of a laboratory diagnostic pathway for the diagnosis of diabetes mellitus](https://example.com/pathway_diagram)

**Figure 1** Example of a relatively simple diagnostic pathway for the diagnosis of diabetes mellitus (translated from ref. [4]). The pathway follows the recommendations of the American Diabetes Association (ADA) as modified by Deutsche Diabetes Gesellschaft (DDG). FPG, fasting plasma glucose; OGTT, oral glucose tolerance testing; 2h-PG, Plasma glucose level 2 h after OGTT. For risk factors of diabetes see ADA recommendations [7].
international guidelines, for example, those of the American Diabetes Association [7], and are implemented as standard operation procedures in the clinical setting.

Another beneficial field of application is the differential diagnosis of specific syndromes like porphyrias (Figure 2), which by their rarity and/or complexity are prone to either under- or over-diagnostics.

Although early definitions of diagnostic pathways date back into the 1970s [8], there is still some confusion with regard to overlapping terms such as “recommendations”, “guidelines” or “directives” [9]. All of them are closely related, but describe different aspects of a complex topic with many facets. A frequent saying is that directives must, guidelines should and

![Figure 2](translated from ref. [4]).

Typically, porphobilinogen/creatinine ratios urine are increased by factor 5 and may persist for at least 1 week after onset of symptoms. A normal quantitative porphobilinogen level excludes porphyria as the cause of an acute abdominal crisis (right branch of the decision tree). Three major inherited diseases can underly acute porphyrias (middle branch): Acute-intermittent porphyria due to mutations in porphobilinogen (PBG)-deaminase [=hydroxymethylbilansynthase (HMBS)], porphyria variegata due to mutations in protoporphyrinogen-oxidase (PPOX) and hereditary coproporphyria due to mutations in coproporphyrinogen-oxidase (CPOX). The lower part of the diagram describes genetic (HMBS, PPOX, CPOX) and biochemical tests (e.g., PBG desaminase activity and plasma fluorescence), details of which can be found in ref. [4].
recommendations can be obliged [4]. For more definitions see Appendix.

Diagnostic pathways are not identical with any of these terms, but must of course respect regulatory demands (directives) and evidence-based facts (guidelines) whenever possible. In contrast to guidelines, they are not universally valid but need to be adapted to local requirements and resources. For example, a laboratory diagnostic pathway for NSTEMI (myocardial infarction without ST-elevation in the ECG) may start with a highly sensitive troponin assay [10]; this test should be repeated after 3 h [11], if the result is normal. However, if no sensitive troponin is available (e.g., in a point-of-care situation), the repeat measurement needs to be performed after 6–9 h due to the higher decision limits of conventional troponin assays [10, 11].

Figuratively speaking, diagnostic pathways are comparable to car navigation systems, which are based on street maps (“guidelines”) and respect traffic laws (“directives”), without being one or the other. Although it is usually wise to follow the electronic recommendations, in certain situations it may be life-saving to deviate. And finally another parallel: Diagnostic pathways can be plotted on paper as depicted in Figures 1 and 2 (“street map”), but unless they have been implemented in an electronic system (laboratory or hospital information system), they will not be helpful in daily routine. This is especially true for iterative and comprehensive pathways that try to cover all frequent and rare causes of a syndrome. For example, the stepwise differential diagnostics of icterus covering frequent causes such as infectious hepatitis and then rarer causes such as autoimmune hepatitis, metabolic disorders, intoxications, etc. will lead to a very complex pathway diagram which is difficult to read and to interpret by visual inspection but can be used for navigation if implemented within the laboratory or hospital information system.

Clinical care pathways are usually more complex than their diagnostic counterparts, because they represent frameworks for the inter-professional description and steering of all medical services within the hospital. Formally, they rely mostly on flow charts or swim lanes with time points, responsibilities and decision points [3, 4]. Very often, clinical pathways as well as medical guidelines and directives do not sufficiently take into account current diagnostic developments and issues. In these cases, diagnostic pathways can fill the gap on a local basis, by seeking for consensus among laboratory and clinical experts while respecting evidence, personnel, technical as well as economic resources. For each laboratory-diagnostic pathway in the above-mentioned book [4], an interdisciplinary expert group was formed, consisting of clinicians and laboratory experts.

Paradigm shift

If established broadly, laboratory diagnostic pathways may provoke a paradigm shift in that the end-users (physicians) are no longer faced with the time consuming selection of appropriate laboratory tests. In simple words, ordering a medical condition in the electronic order entry system is the only step required. The system then provides the user with the standard tests that will be analyzed, the respective patient materials to be taken, and the preanalytical specifications to be considered. Additional tests that are required at specific decision points are under the responsibility of the laboratory, acting along the previously consented diagnostic pathways. A recent study confirmed that physicians often feel uncertain about which tests to order (both for clinical and economic reasons), and that they endorse the help of information technology for test selection and even for interpretation of test results [12].

Benefits

It has been shown in rigorous evaluations that clinical pathways have the potential to improve the quality of care [1, 3, 6, 13] and patient outcomes [14]. No such systematic studies have been published so far for diagnostic pathways, but projects are underway in the authors’ institutions. Table 1 presents a list of potential benefits, modified according to [15]. In summary, establishing diagnostic pathways means standardizing diagnostic decision processes according to the best available knowledge. Such an initiative can serve as an integral part of total quality management and internal quality assurance.

The concept of rule-based systems and decision trees came up more than 20 years ago, when large test profiles became available on automated analyzers and computers were increasingly used to regulate the flood of data [16]. The term “reflex testing” [5] was introduced at that time as an antidote to profile testing. It indicated “algorithmic” (i.e., computer based) decision making as opposed to “reflective” decisions made by physicians [17].

The essential benefit of the selective paradigm is statistical in nature: While a shot-gun strategy produces many false positive results, the stepwise approach increases the probability of a suspected diagnosis with each new result, thus reducing the risk of false positives. Diagnostic
pathways ("smart profiles") as described above have an additional advantage over the traditional stepwise ordering process: Since all relevant patient materials are initially available in the laboratory, the whole sequence of appropriate tests can be performed without drawing new specimens and ordering consecutive tests. This makes workflows much smoother and reduces the number of phone calls and other time-consuming activities.

Diagnostic pathways can also help to integrate the laboratory more closely in the medical and administrative process of the hospital, which will boost the effectiveness of medical services with respect to DRG requirements. Most importantly, well-defined pathways make sure that state-of-the-art laboratory tests are ordered, outdated and unnecessary tests are avoided, and that for identical diagnostic issues identical strategies are applied throughout the hospital.

The laboratory can thus contribute to patient outcome and value creation, improve case management by faster and more reliable laboratory results, and finally support DRG coding by delivering the appropriate ICD codes, whenever a defined diagnosis can be attributed to an endpoint in the decision tree.

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The advantage of simplicity is, however, also one of the biggest problems of decision trees. Each branch stands for a yes or no with no graduation in between, for example:

IF troponin is elevated
THEN diagnosis is myocardial infarction.

This rule looks very straightforward, but in reality, the IF part ("troponin is elevated") is not that clear-cut; rather it indicates just a probability for the presence of myocardial infarction. Assuming sensitivities and specificities of around 90% for troponin [11, 20], one out of ten such decisions will be wrong – provided that the prevalence of myocardial infarction in the examined patient population is 50%. If the prevalence is lower, the error rate of positive results will be even worse. In the typical case of a chest pain unit with about 15% MI patients, four out of ten positive decisions will be wrong (positive predictive value PPV = 61%).

Thus, once a wrong decision has been made by the computer, the whole subsequent decision chain will run in the wrong direction. This is the reason, why computer-based algorithm can never take “responsibility” for medical decisions and therefore will never replace the human professional in the laboratory. It remains a human task to ensure correct decisions by regarding the full clinical context rather than just a computer flag.

Table 2 gives an overview of potential drawbacks from an organizational and economic point of view. An important limitation of laboratory pathways is that they are not suited for patients suffering from several diseases at a time and/or showing ambiguous clinical symptoms, because each pathway needs a clear starting point: a well-defined suspicion or a predefined symptom. Another relevant limitation is the lack of evidence for many of the “good old”
laboratory, which have been ordered for decades without really evaluating their cost/efficiency ratio. This opens the door for pathways that have been generated under the pressure of other interests (economy, society, insurances, etc.) with potentially negative health outcomes.

Generating and maintaining laboratory diagnostic pathways requires time, money, personnel – and not to forget endurance. Laboratory decision trees must be developed in close and prudent collaboration between laboratory and clinical physicians, in order to achieve the highest possible quality of evidence in the respective clinical setting. Algorithms plotted solely by the laboratory staff, will not find sufficient adherence in clinical practice. In many cases, the biggest bottleneck is lack of IT support. Although many providers of information systems claim that their products provide rule generators and graphics software for pathway implementation, it often turns out that these tools are not powerful enough and too complicated to handle. Specialized staff with knowledge both in medical diagnostics and information technology is needed, but rarely available.

Finally it should be mentioned that the seeming clarity of well-defined diagnostic pathways provokes the abuse of primarily medical intentions for mere economic purposes. Shortly after the above mentioned book [4] appeared, we observed that administrators allowed only tests to be ordered, which were contained in the published decision trees, while tests required for overall patient management were excluded. Potential abuse is certainly not a good argument against diagnostic pathways, but it must be considered when starting a respective project.

Conclusions and outlook

Diagnostic pathways, if adequately generated and implemented, undoubtedly ensure that patients receive the laboratory test results at the best level of evidence. They represent an essential part of an innovative way to optimize processes in medicine, and contribute to cost, results and performance transparency in health care. Medical decisions are made visible through diagnostic pathways, especially if the technical requirements are given. Particularly under the conditions of DRGs, they allow for a clear determination of which laboratory test has to be used for which question. Moreover, laboratory diagnostic pathways represent an important contribution to the integration of modern disease management in a complex health policy development with finite resources, and thus build a bridge between medical and economic needs in the health care system.

Health care quality policy emphasizes that any diagnostic process should be based on validated outcomes and consequently the best available evidence. However, to date, there is a lack of robust evidence regarding diagnostic tests – especially those, which have been in use for decades – because most studies dedicated to this concept do not meet methodological acceptable standards. The key question therefore is how to evaluate the test results in terms of global clinical outcome, to determine utility and effectiveness of diagnostic rules, and to derive high quality recommendations.

Using tumor markers as an example, McShane et al. [21] stated that fundamental discussion and collaboration between clinical physicians, statisticians and laboratory scientists is essential, in order to select the best markers out of a large number of potential candidates for beneficial guidelines. In their study, they described a specific review process called REMARK (REporting recommendations for tumor MARKer prognostic studies). In essence, only studies should be mentioned and included in a review, which are build upon a certain framework of quality attributes such as study-design, statistical methods, or patient collective. Only out of a combination of such high qualitative data suitable diagnostic pathways should be generated.

Another potent tool to evaluate the potential of a study [22] is QUADAS (Quality assessment of studies of diagnostic accuracy included in systematic reviews). It provides a list of requirements for a study to be fulfilled. The respective 14 questions can be answered with yes, no or maybe, thus leading to very comprehensible and illustrative recommendations. With this kind of instrument, it should be possible to bring more light into the process of developing new diagnostic pathways.

Finally, a case study based on GRADE (Grading of Recommendations Applicability, Development and Evaluation), tried to establish clinically feasible guidelines for cow milk allergy in cooperation with the World Allergy Organization [23]. This case showed how important but also how time consuming and complex it is to develop a constructive and consistent guideline. Aiming at evidence based medicine, it must be our ambition despite all barriers and pitfalls to construct reasonable, practicable and
innovative guidelines for clinical physicians, out of a flood of studies, to generate high standard diagnostic pathways.

Applying such tools is not an end in itself. The ultimate goal must be to reduce residual risks of any diagnostic decision for patients and physicians, all the more with regard to some negative experience made after the introduction of DRGs in other countries (e.g., increase in the discharge of unstable patients and increasing release to nursing facilities) [24]. Fears that are based on catchwords such as limiting the freedom of diagnostic ordering must be taken seriously and considered in the light that many hospital patients suffer from multifactorial complex diseases—a condition that cannot be dichotomized in the simple diagram of a diagnostic pathway. To improve this situation, better multivariate algorithms and more sophisticated software packages such as support vector machines [25] are needed, which are currently under development especially in the bioinformatics community [http://www.dgkl.de (AG Bioinformatik)].

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Appendix: Definition of complementary terms

Directives are compulsory rules for acts of commission or omission, released by a legitimate institution. The infringement entails defined sanctions, in particular in accordance with social and professional legislation. The most famous directive for laboratory diagnostics in Germany is has been published by the Bundesärztekammer (RiliBÄK) and contains instructions for quality management.

Guidelines are systematic developed aids for decision making for an appropriate medical approach in each single case. They are not compulsory, but rather practice orientated corridors for decisions and actions. A German consortium of scientific medical expert panel (AWMF) provides more than 700 guidelines on the internet (www.awmf.org/leitlinien/leitlinien.html) at three levels of evidence:

- S1: Recommendations by experts
- S2k: Guidelines based on consensus
- S2e: Guidelines based on evidence
- S3: Guidelines based on consensus and evidence

Recommendations, in this definition, are the weakest form of guidelines.

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