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# A Framework for Case Simulation Surveys: Advancing Clinical Diagnosis Decision-Making

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High Yield Medical Reviews

## Introduction

Case simulation surveys are tool that can enhance diagnostic criteria of rare pathologies. This narrative review presents an approach to developing such surveys, highlighting the need for standardized methods in studying rare and complex pathologies to improve patient outcomes.

## Methods

An in-depth literature review was conducted using PubMed with search terms: “Case Simulation Survey”, “Decision Analysis,” “Forced-Choice,” “Classification Criteria”, “Giant Cell Arteritis”, “Systemic Lupus Erythematosus”, “Systemic Sclerosis”, “Validity”, “Reliability”. These terms were chosen to cover a broad range of relevant literature on decision-making frameworks and diagnostic criteria development. Studies on systemic sclerosis and systemic lupus erythematosus were selected to illustrate complex conditions with which case simulation surveys are effective. The methodology includes: 1) Reviewing literature to identify clinical characteristics; 2) Designing a representative base case; 3) Developing case variations; 4) Piloting the survey with experts; and 5) Analyzing results statistically.

## Results

Case simulation surveys were effectively applied in studies of systemic sclerosis and systemic lupus erythematosus. From these examples, we identified key elements and best practices that contributed to developing a more standardized approach. This included designing a base case, systematically developing case variations, and piloting the surveys with expert audiences. This iterative process addressed challenges such as case specificity and the oversight of rare presentations, resulting in a more reliable methodology. This paper discusses these advancements, demonstrating how the standardized methodology enhances the consistency and applicability of case simulation surveys in clinical research.

## Conclusion

Systematically developed case simulation surveys are powerful tools for improving diagnostic techniques and classification criteria. They enable researchers to study clinical decision-making in controlled environments and front-line physicians when confronting rare diseases, significantly contributing to the refinement of diagnostic criteria and treatment protocols.

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## INTRODUCTION

There is a lack of standardized approaches for a number of rare pathologies; specifically, diagnosing and managing these diseases can be difficult, especially for the physicians who are first to confront these pathologies. Roughly 30 million people in the United States are affected by rare diseases.[1] Moreover, since many conditions can have unique and varying presentations, it becomes difficult for healthcare professionals to make a definitive diagnosis. As a result, physicians must rely on their prior experience to diagnose and treat these obscure pathologies. For example, systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, polymyositis/dermatomyositis, and Sjögren syndrome all have overlapping symptoms.[2]

A potential solution to help ameliorate this issue case simulation surveys. Case simulation surveys are studies used by researchers to develop a framework for diagnosing specific diseases through expert opinion. These survey studies create simulated clinical scenarios where the perspectives of expert physicians can be analyzed based on their decisions in a variety of clinical scenarios. These different clinical scenarios present a wide array of presentations of a specific pathology.

The initial step in a case simulation survey study involves utilizing information garnered from a literature review of the pathology of interest. The literature review is vital to formulating simulations that are realistic and accurately test the diagnostic and management skills of expert physicians. Using relevant presentation factors learned from the literature review, researchers can create simulations that have both usual and unique presentations of a specific disease.

Overall, the goal is to create a case simulation that challenges experts in their diagnosis decisions in a variety of circumstances. As a result, this ensures a complete evaluation of these experts' decision reasoning. Diagnosis of a rare disease can provide influential benefits for patients such as allowing patients to enroll in promising clinical trials as well as preventing them from ineffective treatments.[3]

## METHODS

To garner background information for this narrative review, a literature review was conducted using PubMed. Search terms including "Decision Analysis," "Forced-Choice," and "Classification Criteria" were used in order to best garner a wide variety of relevant literature on decision-making frameworks and diagnostic criteria development. More specifically, research studies on the topic of systemic sclerosis and systemic lupus erythematosus were chosen to depict complex conditions where case simulation surveys have been effective in the past. Lastly, giant cell arteritis was identified as a pathology that could be used in a case simulation survey as there is a multitude of information and data on diagnostic criteria for it. The overall methodology for a case simulation survey study includes (detailed further in the supplementary figure) 1) Literature Review for Clinical and Presentation Characteristics; 2) Designing the Base Case; 3) Developing Case Variations; 4) Piloting the Survey; and 5) Analysis Considerations. These steps are described in further detail in the following section.

## STEPS FOR DEVELOPING CASE SIMULATION SURVEYS

### 1. LITERATURE REVIEW FOR CLINICAL CHARACTERISTICS

The first step in conducting a case simulation survey study is conducting a literature review to obtain a comprehensive understanding of the desired disease of study. A literature review allows researchers to identify vital clinical symptoms, signs, and results of a specific pathology. Furthermore, any pre-existing diagnostic criteria should be utilized to lead the study. For example, the paper by Van der Geest illustrates this process for giant cell arteritis (GCA). The researchers performed a systematic review and meta-analysis of the diagnostic characteristics of GCA.[4] When more typical features such as headache are not present, diagnosis of GCA can be difficult. Early diagnosis is crucial to best avoid vision loss in GCA.[5,6] Studies such as the one by Van der Geest offer verifiable data on symptoms and laboratory results offering valuable insights into diagnosis of a specific disease. Existing diagnostic criteria provide a foundation for designing a "base case" for case simulation survey studies. Systematic reviews and meta-analyses are highly important in supplying a detailed summary and analysis of the condition studied because they provide a verifiable and statistically sound basis for how to design the initial base case. Further, these systematic reviews and meta-analyses provide researchers an evidence-based foundation for how they will develop their case simulation survey. Systematic reviews and meta-analyses are objective research methods that gather evidence across multiple articles and provide a reliable, unbiased summary of existing research on a specific topic.[7] In addition, they combine effect estimates from multiple studies to improve statistical power and precision.[7] The base case is the initial scenario that serves as a benchmark, providing a point of comparison to evaluate the effects of changes in variables or conditions in other simulated scenarios.

In the study by Van der Geest, by analyzing the contribution of each feature to the likelihood of diagnosing GCA, the researchers provide a detailed assessment of how different factors influence the diagnostic process and likelihood of having GCA.[4] The study provides likelihood ratios for specific features, guiding clinical decision-making. Further, the systematic review is optimal for creating a case simulation survey study for GCA as it provides a thorough foundation for diagnosis by describing relevant symptoms and laboratory results.[4] Presentation factors include patient's demographics, (e.g., older age (>50 years old), Caucasian, female), symptoms (e.g., headache, scalp tenderness, jaw and limb claudication, visual phenomena, shoulder and hip girdle stiffness, etc.), patient's signs (e.g., elevated ESR and/or CRP, pallid optic disc edema), and imaging abnormalities (e.g., temporal artery abnormalities on temporal

artery ultrasound, aortitis).[4] On the other hand, presentation factors such as being younger than 70 years old,[4] being of Asian origin,[8] or being a male[9] lower the likelihood of having GCA. Certain presentations of GCA make diagnosis difficult because of the overlap with other pathologies such as polymyalgia rheumatica,[10] and the American College of Rheumatology's 1990 criteria for classifying GCA in research studies are not suitable for clinical diagnosis.[11,12] Therefore, a case simulation survey is a valuable tool for enhancing diagnostic methods for GCA. For less common diseases lacking such comprehensive reviews, researchers may need to conduct their own systematic reviews and/or meta-analyses to develop accurate simulation tools. Researchers can do this by analyzing pre-existing studies to generate a base line for the selected pathology.

## 2. DESIGNING THE BASE CASE

The base case is the initial primary scenario and serves as the starting point for the study. It is crucial that the base case is a realistic and representative scenario for the disease being studied. The base case typically exemplifies a 'textbook presentation' of a condition. This scenario typically illustrates classic symptoms, laboratory results, and more that are widely recognized in medical literature. Research teams may use real patient data if relevant and appropriate to the studied disease, although not necessary.

The base case should cover a multitude of variables that include common symptoms and signs of a disease presentation that depicts a complete scenario of how the condition typically presents. For example, in the case of systemic lupus erythematosus (SLE), anti-dsDNA and anti-Sm antibodies are the most common elevated autoantibodies that present with SLE providing a significant role in diagnosis. On the contrary, anti-nuclear antibody (ANA) is a very sensitive antibody for diagnosing SLE,[13] but some patients with SLE do not have a positive ANA. Further, there have been reported issues about ELISA testing of ANA.[14-17] Through the incorporation of multiple common signs and symptoms into the base case, researchers can effectively display an accurate image of a disease in order to test experts' understanding of a specific pathology.

Moreover, the base case serves as a control scenario against which variations are modified and compared. Although the base case is realistic and presents the most common scenario seen in the real world, case variations should be made from the base case. These case variations allow greater insight into more complex and rare cases of a pathology. In these case variations, symptoms may overlap with other conditions or diseases as well as differ from established clinical patterns. The base case and subsequent case variations become a vital tool in medical education and practice. They aid these expert physicians and other healthcare professionals traverse the nuances of difficult diseases as well as refine and improve their diagnosis skills in the real world as each patient's situation is unique.

Potential categories to include in the base case are symptoms, labs, imaging, treatment strategy, and a more miscellaneous category for other considerations specific to a pathology. Overall, the base case is detailed but not too complex to allow for significant diagnosis decision-making while still being comprehensible thus allowing focus on the critical features.

## 3. DEVELOPING CASE VARIATIONS

The following step is to develop case variations. The purpose of creating case variations is to identify how specific changes in patient symptoms or lab results affect the diagnosis of the specific disease. Changes to these case variables should be single-variable changes in order to isolate and understand the impact of each factor on the likelihood of disease.[18] Through altering one variable at a time, researchers can distinctly observe how that specific factor influences the presentation of a condition. Each case variation should remain clinically relevant and reasonable to effectively answer the desired research questions.

Case variations can range from simple cases to more challenging ones. Simple variations can consist of direct changes such as minor alterations in symptoms or laboratory results. These still mimic typical presentations of the disease to ensure that the expert physicians can still recognize the pathology even when there are slight differences in presentation. On the contrary, more challenging variations present complexities that challenge test the expert's ability to diagnose or treat multifaceted or more unique scenarios. One way that this may manifest is having overlapping symptoms with other diseases, atypical progression patterns, or uncommon responses to treatment. Variations can either be created by the research team or examples from real patient data. If the base case is a created one rather than real patient data, then the case variations should also be created and vice versa thus ensuring the reliability of the analysis.

For example, a case variation for SLE can include more rare symptoms or laboratory results. Some of the more common symptoms and laboratory results may include malar rash, photosensitivity,[19] positive anti-dsDNA and anti-Sm antibodies.[20] However, some more rare symptoms that could be included as case variations include: overt myositis,[21] shrinking lung syndrome,[22] aseptic meningitis, and chorea. More unique laboratory results could be anti-centromere, anti-topo I, and more.[23]

Researchers and expert physicians can gain a better and more comprehensive understanding of a pathology through the use of both simple and complex case variations. This will provide these expert physicians the tools to face unique challenges in real-world clinical practice.

## 4. PILOTING THE SURVEY

Prior to implementing the case simulation survey, researchers must conduct a pilot study. However, even before this, researchers must first obtain Institutional Review Board (IRB) approval and other relevant research committees. Obtaining this approval involves submitting an in-depth research protocol that outlines the study's objectives, methods, potential risks, and ethical considerations. Any questions or concerns made by the IRB or other research committees must be addressed by the researchers. More-

over, modifications to the research protocol should be made to comply with the IRB's ethical standards and institutional policies. For example, using real patient data versus examples created by the research team may be a point of contention. The pilot study can begin once the IRB is approved, and other research committees accept. The chief objective of the pilot study is to evaluate the feasibility and functionality of the proposed research methodology. Through the pilot study, researchers can identify any errors in the study that may lead to inaccurate results and data. The pilot study serves as a testing and refining step to ensure the study is functioning correctly.

The target audience chosen for a study is vital as it ensures that the results and data are relevant. The target audience consists of individuals who are seasoned experts in the area or specialty of study. For example, for systemic lupus erythematosus, the target audience should be rheumatologists who have an expertise and focused in diagnosing and treating this autoimmune condition.

Furthermore, researchers can leverage professional societies to connect with the target audience. These professional societies can aid in connecting with experts who are familiar with the complexities of the chosen pathology which also makes them ideal candidates for the survey. These professional organizations often require further approvals and compliance with their own guidelines. As another option, researchers can invite expert physicians to join the study utilizing their experience. This method develops classification criteria for complex conditions. For example, Johnson et al. used a systematic approach to create a classification criterion for systemic sclerosis. The paper by Johnson et al. utilized expert consensus to reduce weight criteria using a standardized instrument and forced-choice method.[24] Through selecting an appropriate audience, the results of the case simulation survey study can be more thorough and reliable and provide insightful information that guides clinical diagnosis and management of the disease.

## 5. ANALYSIS CONSIDERATIONS

After the conclusion of the main study, appropriate statistical methods should be selected. A software such as R, SAS, or SPSS can be utilized. The reliability of the case simulation survey can be measured using Cronbach's alpha and intraclass correlation coefficient (ICC) tests.[25] Cronbach's alpha evaluates the internal consistency of items within a scale as well as the inter-relatedness.[26] A larger Cronbach's alpha value above 0.70 suggests good reliability.[27,28] Moreover, ICC measures the consistency of evaluations made by various observers on the same subject. A higher ICC value indicates better reliability.[29,30] For example, a study by Trabelsi utilized both ICC and Cronbach's alpha to validate the reliability of the Athlete Sleep Behavior Questionnaire (ASBQ) to analyze sleep behaviors among athletes.[31] The study found a Cronbach's alpha of 0.72 which indicates an acceptable level of internal consistency while the ICC was 0.88 which suggests a good test-retest reliability.

Some other statistical methods to consider are:

- Descriptive statistics: Participant characteristics and overall response patterns can be summarized. The mean age, gender distribution, and average years of experience of the participating expert physicians are some examples that can be analyzed.
- Inferential statistics: Hypotheses can be tested to derive conclusions about the broader population. For example, an independent sample t-test can be used to compare mean scores between different physicians based on varying levels of experience. Also, a chi-square test can be utilized to analyze the relationship between the physician experts' background and their choices on diagnosis or management.
- Multivariate Analysis: Factor analysis or principal component analysis can be utilized to pinpoint underlying patterns or variables that influence decision-making.

In addition, analysis of variance (ANOVA) with Tukey's method can be used for post hoc analysis. ANOVA is a statistical method used to determine if the means of three or more groups are equal or within one mean of each other.[32] For example, ANOVA can be used to identify if there are significant differences in the diagnosis choices of varying levels of physician experts. When ANOVA indicates that at least one group's mean is different, a post hoc analysis, such as Tukey's Honest Significant Difference (HSD) test, can be used to identify which specific group's mean differs. Tukey's method compares all possible pairs of group means and adjusts for the potential of Type I errors. As a result, confidence intervals are produced to determine significant differences between group pairs.[33,34]

## DISEASES STUDIED USING CASE SIMULATION SURVEYS

In the past, case simulation survey studies have been used on a vast array of diseases and conditions. In 2014, a study done by Johnson et al utilized a case simulation survey to develop a classification criterion for systemic sclerosis.[24] Furthermore, a study by Schmajuk in 2018 re-evaluated classification criteria for systemic lupus erythematosus (SLE) using a case simulation survey.[35] These studies differed significantly in terms of approaches to establishing diagnostic criteria. The paper by Schmajuk on SLE utilized a formal consensus approach with a Delphi exercise, resulting in a comprehensive set of 40 candidate criteria that focused on specific autoantibodies and clinical characteristics.[35] This method consisted of multiple phases of expert consultation to refine the criteria. On the other hand, the study by Johnson et al. on systemic sclerosis utilized multi-criteria decision analysis with 1000Minds software. It emphasized the weighting and ranking of each criterion through forced-choice methods.[24] This approach ensured precise criterion evaluation through the use of detailed analysis and distinct pairwise choices to assign relative weights. Although both studies emphasized the importance of consensus, the study by Johnson et al utilized structured decision analysis for criterion weighting while the paper by

Schmajuk relied on broad expert agreement through iterative expert consultation. These two studies depict the multiple ways to conduct a case simulation survey study. While they had different approaches for developing the diagnostic criteria, each study was tailored to the specific needs and niches of the respective disease.

## CHALLENGES AND LIMITATIONS

Although case simulation survey studies are beneficial, they face some challenges and limitations. Case specificity and reliability is one major challenge. The results of one survey study may not correctly predict the results in another scenario thus limiting the generalizability of the results.

Furthermore, another major limitation is that these studies may not comprehensively represent the range of possible clinical scenarios as they often focus on common presentation characteristics. This can lead to problems as rarer or atypical presentations may be missed potentially leading to confusion among experts. For example, some less common presentations may lead expert physicians to a diagnosis quickly through distinct clues; however, other characteristics can make the diagnosis challenging. One example of this is in giant cell arteritis. Presentations such as temporal artery abnormalities and jaw claudication can lead to a prompt diagnosis, but other unusual symptoms such as isolation vision loss or subtle systemic symptoms may make the diagnosis more ambiguous.[4] Another example is neuroblastoma. Although opsoclonus-myoclonus syndrome (OMS) is a rare symptom, it serves as an important indicator that warrants further investigation for this disease. A paper by Rothenberg et al. stated that while OMS is present in 2-3% of patients with neuroblastoma, neuroblastoma is found in up to 50% of children presenting with OMS.[36] This significant association highlights the vital importance of including neuroblastoma in the differential diagnosis when a child presents with OMS. Conversely, a rare symptom of neuroblastoma is Horner syndrome. Two studies found that 3.5-13% of children with neuroblastoma also had associated Horner syndrome.[37,38] However, there can be many other causes of Horner syndrome such as stroke, chest and neck tumors, surgical procedures in the neck and chest area, and more.[39] This spotlight how some rare symptoms can simplify a diagnosis, while others may confuse and challenge expert physicians.

Furthermore, the results of a case simulation survey are de-contextualized indicating that these simulations are limited to verbal and visual cues as well as summaries. The expert physicians taking these surveys must make clinical diagnoses and management decisions with limited information contrary to what they may be presented with in the real world. This may skew the data and affect the results.[40]

There may be several potential solutions to these problems. Future case simulation surveys could incorporate a more diverse and broader spectrum of presentations emphasizing the importance of developing a wide and all-encompassing range of case variations. Furthermore, in the future, the use of virtual reality may be helpful in providing more context during a case simulation survey into a diagnosis and management scenario. For example, virtual reality can create more realistic patient interactions allowing physicians to also observe body language or facial expressions which may aid diagnosis. Expert physicians would have more clues into a situation which would solve the problem of de-contextualization. Lastly, longitudinal case simulation surveys may be useful to build upon on knowledge gathered from older versions of a survey. This may be done by modifying surveys while generating and identifying new rare symptoms or lab results; this may be able to add on the previous knowledge garnered form older versions of a survey.

## CONCLUSION

Case simulation survey studies can be a valuable tool in medical research to garner insightful information into expert physicians' reasoning processes in diagnoses and management of specific pathologies. The systematic approach to developing these surveys is:

1. Literature review for clinical characteristics
2. Designing the base case
3. Developing case variations
4. Organizing a pilot study
5. Key analysis considerations

Case simulation survey studies allow researchers to study clinical decision-making in a controlled environment. These surveys contribute greatly to research by improving understanding of how expert physicians process clinical situations in both diagnosis and management. By better prioritizing diagnostic criteria and treatment protocols through simulation-based research, healthcare providers may not only improve the accuracy and efficiency of clinical decision-making but also cut down on unnecessary diagnostic testing. As a result, this may lead to reduced costs, quicker and more accurate diagnoses, improved patient care, etc. Overall, case simulation survey studies are a cost-effective research method that improves the accuracy of diagnosis and patient care.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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# SUPPLEMENTARY MATERIALS

## Supplementary material

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