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JAMA Dermatology | Consensus Statement

Isotretinoin Laboratory Monitoring in Acne Treatment
A Delphi Consensus Study

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IMPORTANCE Although isotretinoin may rarely be associated with laboratory abnormalities such as hypertriglyceridemia, the optimal approach to laboratory monitoring is uncertain, and there is wide variation in clinical practice.

OBJECTIVE To establish a consensus for isotretinoin laboratory monitoring among a diverse, international cohort of clinical and research experts in acne.

DESIGN, SETTING, AND PARTICIPANTS Using a modified electronic Delphi process, 4 rounds of anonymous electronic surveys were administered from 2021 to 2022. For laboratory tests reaching consensus (≥70% agreement) for inclusion, questions regarding more time-specific monitoring throughout isotretinoin therapy were asked in subsequent rounds. The participants were international board-certified dermatologist acne experts who were selected on a voluntary basis based on involvement in acne-related professional organizations and research.

MAIN OUTCOMES AND MEASURES The primary outcome measured was whether participants could reach consensus on key isotretinoin laboratory monitoring parameters.

RESULTS The 22 participants from 5 continents had a mean (SD) time in practice of 23.7 (11.6) years and represented a variety of practice settings. Throughout the 4-round study, participation rates ranged from 90% to 100%. Consensus was achieved for the following: check alanine aminotransferase within a month prior to initiation (89.5%) and at peak dose (89.5%) but not monthly (76.2%) or after treatment completion (73.7%); check triglycerides within a month prior to initiation (89.5%) and at peak dose (78.9%) but not monthly (84.2%) or after treatment completion (73.7%); do not check complete blood cell count or basic metabolic panel parameters at any point during isotretinoin treatment (all >70%); do not check gamma-glutamyl transferase (78.9%), bilirubin (81.0%), albumin (72.7%), total protein (72.7%), low-density lipoprotein (73.7%), high-density lipoprotein (73.7%), or C-reactive protein (77.3%).

CONCLUSIONS AND RELEVANCE This Delphi study identified a core set of laboratory tests that should be evaluated prior to and during treatment with isotretinoin. These results provide valuable data to guide clinical practice and clinical guideline development to optimize laboratory monitoring in patients treated with isotretinoin.

Supplemental content

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Isotretinoin is a potent vitamin A derivative primarily used as a first-line treatment for severe acne. Since being FDA approved in 1982, isotretinoin has remained the most effective treatment for the condition, producing long-term acne remission after approximately 6 months of therapy.[1] However, various adverse effects have been reported related to isotretinoin treatment, most commonly mucocutaneous dryness and joint aches, but also more rare and serious adverse effects such as pancreatitis, mood changes, and teratogenicity.[2-4]

In addition, there have been concerns about potential associations between isotretinoin and laboratory abnormalities including hypertriglyceridemia, transaminitis, thrombocytopenia, and leukopenia.[5,6] Concerns about potential serious systemic complications, such as pancreatitis due to hypertriglyceridemia, have led to frequent monitoring of patients' laboratory values.[7,8] Besides pregnancy tests for persons of childbearing potential, the isotretinoin (Accutane) drug label, originally released in 1982, recommends laboratory monitoring of lipids and liver function tests at weekly or biweekly intervals "until the response to Accutane has been established." The drug label also notes that while there have been instances of glucose abnormalities and creatine kinase elevations, the clinical importance and risk of diabetes and rhabdomyolysis, are unknown or unclear.[2,9] However, recent findings suggest that there may be little evidence supporting frequent routine monitoring.[10] Abnormalities identified on routine tests are rare and often do not impact treatment course, and for most cases, abnormalities are mild and transient.[11,12]

In the context of these new data, the optimal approach to laboratory monitoring is uncertain. There is still wide variation in clinical practice, with physicians continuing to frequently monitor laboratory values that may be clinically unimportant or of low clinical value, and no recent consensus standards have been developed.[13] In this study, we used a modified electronic Delphi process to establish a consensus for isotretinoin laboratory monitoring among a diverse, international cohort of clinical and research experts in acne.

Key Points

Question What is the optimal approach to laboratory monitoring for otherwise healthy patients treated with isotretinoin for acne?

Findings In this modified Delphi consensus study administered to 22 international dermatologist experts in acne, consensus was achieved for checking alanine aminotransferase and triglycerides at baseline and peak dose. Consensus was achieved for not checking complete blood cell count or basic metabolic panel parameters, among others.

Meaning Given the wide variation in practice patterns, these results provide data to guide clinical practice and guideline development to optimize laboratory monitoring for patients treated with isotretinoin for acne.

Methods

This Delphi consensus study was approved by the Mass General Brigham institutional review board's Human Research Committee. The modified electronic Delphi survey technique is an established, iterative process in which several rounds of anonymous surveys are presented to guide health care decision-making.[14] This method has already been used in a variety of dermatologic conditions, including pyoderma gangrenosum, scabies, and atopic dermatitis to establish best-practice treatment guidelines and diagnostic criteria.[15-17] After recruiting a panel of experts, an initial survey round is presented in which participants express their own opinions, ideas, questions, and comments. In the following rounds, the anonymous previous participant responses are aggregated, summarized, and subsequently presented to participants to help guide eventual consensus.

We recruited 22 participants, all of whom are board-certified dermatologists participating on a voluntary basis. Participants were selected based on involvement in professional organizations and research related to acne. A diverse international panel was selected, including dermatologists from North America, South America, Europe, Australia, and Asia. Both pediatric and adult dermatologists were included. Upon electronic consent to participation, using a modified electronic Delphi technique, a series of anonymous electronic surveys via Research Electronic Data Capture (REDCap) tools were administered using encrypted email with an overarching goal of achieving consensus among dermatologist acne experts.[18,19]

The study consisted of a total of 4 rounds in which participants were asked to rank whether they would perform core laboratory values at given treatment times on a scale from 1 to 9, with 1 meaning strongly disagree and 9 meaning strongly agree. Responses were then anonymously aggregated using a standardized scoring system in which having at least 70% of responses scoring 7 to 9 indicated consensus in agreement with the statement, at least 70% of responses scoring 1 to 3 indicated consensus in disagreement with the statement, and responses not reaching the 70% threshold indicated no consensus.

For statements lacking consensus, aggregated scores and feedback from participants were presented in the subsequent round for review, and participants were asked to rescore that statement. If consensus was still not reached after 2 iterations, we concluded that there was no consensus regarding that laboratory value. However, laboratory tests in round 3 close to reaching consensus, denoted by at least 60% consensus, were presented again in the fourth and final round (**Figure 1**).

Because of the cost and feasibility challenges of having a live discussion between all participants given the nature of our international study, and because many items that did not reach consensus were related to liver function testing, after the second round, a hepatology specialist was recruited to provide additional feedback to the participants. The hepatologist created a short video regarding the rationale for various laboratory tests in their relation to isotretinoin treatment to further guide ratings in round 3. A detailed flowchart of the round-by-round methodology can be found in the eFigure in the Supplement.

Results

Out of the 22 survey participants, the mean (SD) time in practice was 23.7 (11.6) years with a median (IQR) of 25.5 (15.0-30.0) years; 12 (54.5%) practiced in an academic setting, 7 (31.8%) practiced in private practice, 14 (63.6%) were based in North America, and 4 (18.2%)

Figure 1. Delphi Consensus Methodology

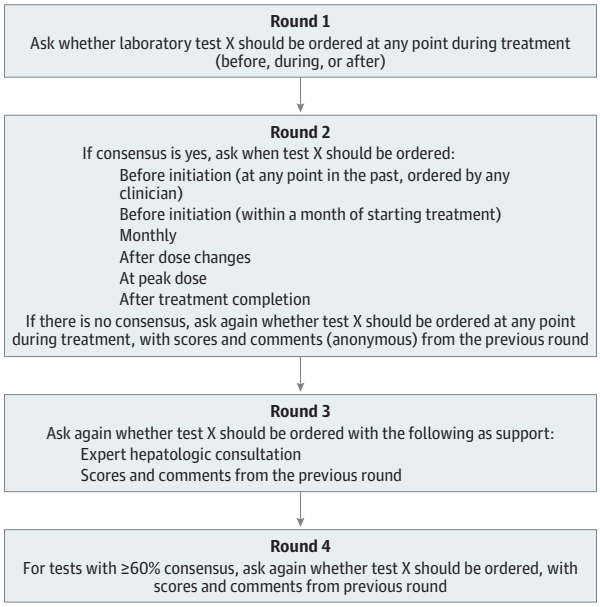


Table 1. Survey Participant Demographics

Characteristic	No. (%) (N =22)
Sex	
Male	10 (45.5)
Female	12 (54.5)
Time in practice, y	
Mean (SD)	23.7 (11.6)
Median (IQR)	25.5 (15.0-30.0)
Practice setting	
Academic	12 (54.5)
Nonacademic	1 (4.5)
Private practice	7 (31.8)
Multiple	2 (9.1)
Geographic region	
North America	14 (63.6)
South America	1 (4.5)
Europe	4 (18.2)
Asia	2 (9.1)
Australia	1 (4.5)

were based in Europe (**Table 1**). Round by round participation rates were as follows: 100% in round 1, 95.5% in round 2, 90.5% in round 3, and 100% in round 4.

After 4 rounds, consensus was reached for most of the laboratory tests. The only tests that reached consensus for inclusion were alanine aminotransferase (ALT) and triglycerides, which should both be tested once within a month of starting isotretinoin treatment (89.5% for ALT; 89.5% for triglycerides) and a second time at peak dose (89.5% for ALT; 78.9% for triglycerides). For ALT and triglycerides, testing monthly (76.2% not for ALT; 84.2% not for triglycerides) and after treatment completion (73.7% not for ALT; 73.7% not for triglycerides) reached consensus for exclusion. Likewise, among the liver function tests, there was consensus around excluding gamma-glutamyl transferase (GGT) (78.9%), serum bilirubin (81.0%), total protein (72.7%), and serum albumin (72.7%). Metabolic laboratory tests that reached consensus for exclusion included sodium (81.8%), potassium (81.8%), calcium (81.8%), bicarbonate (81.8%), chloride (81.8%), fasting blood glucose (76.2%), blood urea nitrogen (77.3%), and creatinine (81.8%). The other tests with consensus for exclusion were low-density lipoprotein (LDL) (73.7%), high-density lipoprotein (HDL) (73.7%), all hematologic laboratory tests, and C-reactive protein (77.3%). The tests with no consensus were aspartate aminotransferase (AST), alkaline phosphatase, creatine kinase, and total cholesterol (**Table 2**). Detailed round-by-round consensus results can be found in the eAppendix in the Supplement.

Discussion

Our international Delphi consensus study achieved consensus on a simple, standardized approach to laboratory evaluation for patients taking isotretinoin for acne (**Figure 2**). Given the longstanding ambivalence surrounding isotretinoin laboratory monitoring, our results provide an integral step forward. Specifically, we recommend that for generally healthy patients without underlying abnormalities or preexisting conditions warranting further investigation, it is sufficient to test ALT and triglycerides once at baseline, ideally within a month prior to treatment initiation, and a second time at peak dose. Other tests such as complete blood cell counts and basic metabolic panels as well as specific laboratory tests such as GGT, serum bilirubin, total protein, serum albumin, LDL, HDL, and C-reactive protein should not be routinely monitored. We suggest that these results, derived from experts from 5 continents and representing a diversity of practice settings, are applicable globally.

Although there are existing guidelines for the management of acne, such as the American Academy of Dermatology work group guidelines released in 2016 and the NICE guideline published in 2021, the specific recommendations surrounding laboratory monitoring frequency are nonstandardized and often nonspecific.[20,21] In fact, despite increasing evidence that routine laboratory monitoring may hold low clinical utility, one study found that between 2008 and 2016, routine monitoring of complete blood cell counts remained unchanged, whereas monitoring of liver function and lipids only decreased slightly.[13] Our results apply findings from recent literature and are in accordance with recent studies that have recommended against excessive laboratory monitoring. For instance, several studies in both teenagers and adults have shown that routine complete blood cell count laboratory tests are unnecessary without suspicion of an underlying abnormality and that rare abnormalities, if present, either resolved or remained stable without clinical impact on treatment.[5,22,23] Likewise, liver function tests and lipid panels ordered at baseline and after 2 months of therapy were deemed sufficient if the clinical context and results do not suggest potential abnormalities.[22,23]

Additional research is required to determine best practices for laboratory measures that did not reach consensus. For example, there is uncertainty surrounding the clinical value of monitoring AST, especially given that AST may be less specific than ALT.[24] Regarding alkaline phosphatase, although some studies recommend monitoring, reported changes are typically minor and of unclear importance.[24,25] Likewise, although some clinicians recommend

Table 2. Guidelines for Isotretinoin Laboratory Monitoring

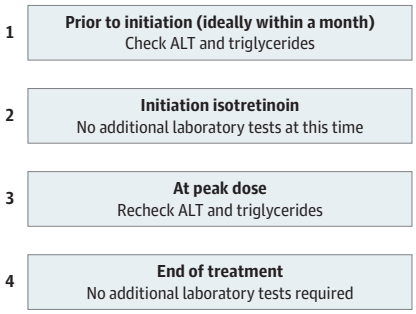
	Recommendation, % consensus[a]		
Laboratory tests	Include	No consensus	Exclude
Liver function tests			
ALT	89.5 (prior to initiation within 1 month of starting treatment)	52.6 (for include prior to initiation at any point in the past)	76.2 (monthly)
	89.5 (at peak dose)	47.4 (for include after dose changes)	73.7 (after treatment completion)
AST	NA	47.4 (for include at any time)	NA
Alkaline phosphatase	NA	47.4 (for include at any time)	NA
GGT	NA	NA	78.9
Serum bilirubin	NA	NA	81.0
Total protein	NA	NA	72.7
Serum albumin	NA	NA	72.7
Metabolic tests			
Sodium	NA	NA	81.8
Potassium	NA	NA	81.8
Calcium	NA	NA	81.8
Bicarbonate	NA	NA	81.8
Chloride	NA	NA	81.8
Fasting blood glucose	NA	NA	76.2
Blood urea nitrogen	NA	NA	77.3
Creatinine	NA	NA	81.0
Creatine kinase	NA	57.9 (for exclude)	NA
Lipid panel			
Triglycerides	89.5 (prior to initiation within 1 month of starting treatment)	52.6 (for include prior to initiation at any point in the past)	84.2 (monthly)
	78.9 (at peak dose)	42.1 (tied for include and exclude after dose changes)	73.7 (after treatment completion)
LDL	NA	NA	73.7
HDL	NA	NA	73.7
Total cholesterol	NA	47.4 (for exclude)	NA
Hematologic tests			
White blood cells	NA	NA	76.2
Hemoglobin	NA	NA	76.2
Hematocrit	NA	NA	76.2
Red blood cells	NA	NA	76.2
Platelets	NA	NA	76.2
Mean platelet volume	NA	NA	72.7
Differential (% lymphocytes, eosinophils, neutrophils, or other)	NA	NA	76.2
Mean corpuscular volume	NA	NA	85.7
Red cell distribution width	NA	NA	72.7
C-reactive protein	NA	NA	77.3

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not applicable.

[a] For laboratory tests with no consensus, the percentage shown, which is for either inclusion or exclusion, represents the most popular recommendation. Unless specific time points are specified (eg, prior to initiation), inclusion refers to evaluating that laboratory parameter at any time throughout isotretinoin therapy.

monitoring creatine kinase out of caution owing to potential elevation, the importance of these elevated levels is unclear.[26] True rhabdomyolysis during isotretinoin treatment is exceedingly rare, and given the nonspecific nature of creatinine kinase, the rate of false positive tests may limit its potential usefulness in detecting rhabdomyolysis.[27,28] Nonetheless, given rare case reports of rhabdomyolysis, some of which are also associated with strenuous physical activity, there may be a lower threshold to testing for certain populations such as competitive athletes.[9] For total cholesterol, although laboratory value changes are common and expected, it is unclear whether these changes are actionable and warrant routine monitoring.[22,29] Future research, including larger patient validation studies representing diverse patient populations, may provide better clarity regarding the utility of these tests.

Figure 2. Laboratory Monitoring Recommendations for Isotretinoin[a]



[a] These recommendations only apply for generally healthy patients without underlying abnormalities, preexisting conditions, or clinical context warranting further investigation.

ALT indicates alanine aminotransferase.

Because current laboratory monitoring practices for isotretinoin often involve more frequent testing than our consensus recommendations,[13] our results have the potential to decrease the quantity and frequency of laboratory testing. The cost of current testing practices, which also includes indirect costs such as missed time from work or other obligations, coupled with the inconvenience of frequent clinic visits, may dissuade patients from starting or continuing isotretinoin therapy, which can directly translate to poorer patient outcomes.[13] Likewise, frequent unnecessary monitoring poses a substantial psychosocial burden for patients, who may experience not only worry about potential rare abnormalities showing up on laboratory tests but also pain and distress surrounding phlebotomy, especially in younger patients.[30] By eliminating potentially wasteful testing, the pain, fear, and cost for patients being treated with isotretinoin can be reduced.

Although the results of our consensus recommend limited triglyceride and liver function screening at baseline and peak dose, it is important to continuously reassess these recommendations as new evidence accumulates. Pancreatitis in the setting of isotretinoin for acne is rare, and many cases are not associated with hypertriglyceridemia.[13,31] Similarly, there is limited evidence that isotretinoin is associated with meaningful hepatic injury and one study found liver function testing abnormalities are just as common prior to initiation of isotretinoin as on therapy suggesting these abnormalities are not related to treatment.[13]

Limitations

This study had some limitations, and these findings must be interpreted in the context of the study design. Given the international distribution of participants, it was not logistically possible to facilitate live discussions between rounds to help guide consensus. Instead, asynchronous sharing of results and comments from each round were used to facilitate deliberation and consensus. Furthermore, this study relies on the opinions of a relatively small group of participants. Although these dermatologists are all respected experts in treating acne, their opinions may or may not be representative of all clinicians and practice settings. Although screening may identify abnormalities unrelated to isotretinoin (eg, underlying hematologic disorders), the utility of screening asymptomatic, otherwise healthy individuals beyond existing recommendations is uncertain.

Future Research

There were several laboratory tests that still did not reach consensus, highlighting areas in need of future research to identify the potential usefulness of these studies. For many of these tests, there is scarce knowledge surrounding appropriate monitoring practices, and monitoring frequency may often be dependent on a clinician's personal preferences, caution for safety, and specific patient population.

The results of this study are intended to guide appropriate clinical decision-making. Although our recommendations cannot replace clinical judgement based on the unique circumstances of individual patients, we believe they provide a framework for management of a typical, otherwise healthy patient being treated with isotretinoin for acne. More routine monitoring, or reduced monitoring, should be considered on a case-by-case basis accounting for the unique medical history, circumstances, and baseline abnormalities, if present, of each patient.

Conclusions

This modified electronic Delphi consensus study among dermatologists with expertise in acne provides data to guide clinical practice and guideline development to optimize the use of laboratory monitoring for patients treated with isotretinoin. For generally healthy patients with no underlying abnormalities or preexisting conditions that warrant further investigation, we recommend only to test ALT and triglycerides once at baseline, ideally within a month prior to treatment initiation, and a second time at peak dose. Reducing unnecessary laboratory monitoring may help decrease the pain, fear, and direct and indirect costs experienced by patients being treated with isotretinoin for acne.

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Author Contributions: Drs Mostaghimi and Barbieri had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Barbieri and Mostaghimi contributed equally to the work.
Concept and design: Xia, Han, Faletsky, Baldwin, Dréno, Goh, Kircik, Mann, Webster, Thiboutot, Zaenglein, Barbieri, Mostaghimi.
Acquisition, analysis, or interpretation of data: Xia, Han, Baldwin, Beleznay, Bettoli, Goh, Stein Gold, Gollnick, Herane, Kang, Kircik, Nast, Oon, See, Tollefson, Webster, Zip, Tan, Tapper, Thiboutot, Zaenglein, Barbieri, Mostaghimi.
Drafting of the manuscript: Xia, Stein Gold, Oon, Zip, Barbieri, Mostaghimi.
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