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Modernizing Clinical Trial Eligibility Criteria: Recommendations of the ASCO-Friends of Cancer Research Laboratory Reference Ranges and Testing Intervals Work Group

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The opinions expressed in this article are those of the authors and do not necessarily reflect the views or policies of the authors' affiliated institutions.

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Abstract

Purpose: In clinical research, eligibility criteria promote patient safety and optimize the evidence generated from clinical trials. However, overly stringent eligibility criteria—including laboratory requirements—may limit enrollment, resulting in delayed trial completion and potentially limiting applicability of trial results to a general practice population.

Methods: Starting in 2018, a working group consisting of experts in direct patient care, the U.S. Food and Drug Administration (FDA), industry, and patient advocacy developed recommendations to guide the optimal use of laboratory reference ranges and testing intervals in clinical trial eligibility criteria and study procedures. The working group evaluated current eligibility criteria across different clinical trial phases and performed a literature review to evaluate the impact of and justification for laboratory test eligibility requirements and testing intervals in clinical trials. Recommendations were developed based on the goals of promoting safety and optimizing the evidence generated, while also expanding eligibility and applicability, and minimizing excess burden of trial participation.

Results: In general, we found little variation over time and trial phase in laboratory test requirements, suggesting that these eligibility criteria are not refined according to ongoing clinical experience. We propose recommendations to optimize the use of laboratory tests when considering eligibility criteria.

Conclusions: Tailoring the use of laboratory test requirements and testing intervals may increase the number and diversity of patients in clinical trials and provide clinical data that more closely represents the general practice populations.

Keywords

Clinical trials; access; equity; generalizability

INTRODUCTION

Clinical trial enrollment has become more challenging over the years in part due to increasing number and complexity of eligibility criteria and study requirements. From 2001 to 2015, trial endpoints, eligibility criteria, and procedures steadily increased.^{1,2} An evaluation of Eastern Cooperative Oncology Group (ECOG) lung cancer protocols revealed a median increase in number and complexity of eligibility criteria from 17 in 1986–1995 to 27 in 2006–2016.³ Appropriate and relevant eligibility criteria are necessary to ensure the safety of patients participating in a clinical study and to allow for interpretability of the clinical study results.⁴ However, overly stringent eligibility criteria may unnecessarily limit enrollment, resulting in delayed trial completion, and limiting generalizability of the research results to a broader practice population. Eligibility for clinical trials should be recognized as a distributive justice issue for individual patients and for vulnerable populations.⁵ Balancing the need for modernized eligibility criteria that with patient safety requires careful review and planning of clinical trial protocols and eligibility criteria.

In 2016, the American Society of Clinical Oncology (ASCO) and Friends of Cancer Research (*Friends*) initiated a joint project to evaluate eligibility criteria in oncology clinical trials and to investigate potential strategies that could expand trial eligibility while maintaining patient safety.⁶ This initial effort resulted in the development of key recommendations that catalyzed efforts to improve the applicability and accessibility of clinical studies to patients with brain metastases, HIV infection, younger age, organ dysfunction, and prior/concurrent malignancies.^{6–10} However, additional barriers and opportunities remain. Follow-up activities were conducted to identify and prioritize additional criteria that may hinder the rate of trial accrual and unnecessarily restrict patient access to investigational therapies.

Laboratory tests represent one of the most commonly employed categories of eligibility criteria in clinical trials. For instance, minimum renal and hepatic function may be required for therapies that are either metabolized by or pose toxicity to these organ systems. Similarly, threshold blood counts provide a margin of safety for myelosuppressive treatments. Despite this clear rationale, there is obvious potential for unintended consequences. For instance, in oncology, the majority of patients are older, a population in which some degree of organ dysfunction is quite common but rarely has clinical consequences. It follows that a recent study found that strict renal and hepatic function requirements were one of the most common reasons for excluding potential patients from clinical trials.¹¹ While not every patient will be a candidate for a clinical trial, the exclusion of patients for what can often be arbitrary reasons, thereby diminishing the desire for those involved to enroll on clinical trials. Laboratory abnormalities may also represent reversible manifestations of the underlying malignancy. ASCO and *Friends* established a working group to understand current practices related to clinical trial laboratory test requirements and intervals. The group also assessed whether reasonable changes could be recommended while preserving patient safety and study scientific integrity. The scope of work did not encompass tumor tissue requirements or biomarker testing for clinical trial enrollment as they require additional considerations beyond the use of laboratory tests as eligibility criteria.^{12,13}

PROCESS

To inform our recommendations related to laboratory test requirements and testing intervals, we reviewed eligibility criteria from a sampling of recently submitted or active cancer clinical trial protocols from diverse sources. Specifically, we included protocols from (a) a clinical practice setting (Sarah Cannon Research Institute; industry-sponsored trials activated January 2018–May 2019; N=97); (b) an industry sponsor (AstraZeneca; late-phase oncology trials active in 2018; N=13); and (c) a regulatory authority (FDA; applications submitted May 2018–May 2019; N=13). The following information was collected and summarized: disease under study; trial phase; class of therapy (targeted/small molecule, immunotherapy, chemotherapy, or combination therapy); eligibility thresholds for bone marrow, renal, and hepatic function; requirements for transfusion- and growth factor- free periods; and coagulation parameters.

Separately, we reviewed 2019 oncology FDA approvals and identified 26 approvals based on randomized phase 3 clinical trials. Published manuscripts supporting 23 of the 26 approvals

were retrieved (as of March 2020) and the eligibility criteria specifics for each trial were extracted from the manuscript supplementary material (Supplementary Table S1).

FINDINGS

Evaluation of Eligibility Criteria in Clinical Trial Protocols

Table 1 broadly describes the characteristics of the clinical trials included in our assessment of laboratory test criteria. Over a 100 industry sponsored trials were represented in the trial review and 13% of the trials only enrolled patients with a hematologic malignancy.

Figure 1 displays the laboratory test-based eligibility criteria for the 107 solid tumor trials included in our analysis. In general, we observed the greatest heterogeneity for renal function, even within a single drug class. For instance, among immune checkpoint inhibitor trials, creatinine clearance (CrCl) requirements were almost equally distributed among 30, 40, 50, and 60 mL/min. The justification for such variation is not readily clear, as these drugs tend to undergo similar metabolism and excretion and have similar rates of nephrotoxicity. It is also noteworthy that the most common minimum platelet count requirement was 100,000/ μ L for all three drug classes, even though thrombocytopenia occurs almost universally with cytotoxic chemotherapy but in well under 5 percent of patients treated with immune checkpoint inhibitors. Similarly, hemoglobin eligibility requirement was 9 g/dL for almost all trials, with anemia a common toxicity with cytotoxic agents but a rare event with immunotherapy.

Hepatic function exceptions for patients with suspected Gilbert's syndrome and liver metastases were employed for most clinical trials (66% and 71%, respectively). The guidelines for patients with Gilbert's syndrome ranged widely: some trials allowing for a total bilirubin of up to 3 to 5x upper limit of normal (ULN) and a direct bilirubin up to 1.5 x ULN; in some cases, no threshold was specified. Additionally, the existence of such exceptions raises the question whether laboratory test thresholds could be relaxed more broadly. That is, if a therapy is considered safe in a patient with elevated hepatic transaminase levels due to liver metastases, might it also be safe in a patient with liver dysfunction due to another reason? As expected, we found that bone marrow function (i.e., minimum blood counts) criteria have different thresholds if included in hematology malignancy trials (Figure 2).

Importantly, our findings are almost identical to earlier reviews by the FDA and by the ASCO and *Friends* working group.¹⁴ This lack of variation over time suggests the possibility that laboratory test-based eligibility criteria template language may be carried forward despite the accumulation of additional clinical experience—on trials or after approval. We noted a similar phenomenon when tracking clinical development across trial phases. Our review of published material (Supplementary Table S1) of 23 of the 26 oncology drugs approved by FDA based on randomized phase 3 trials in 2019 demonstrated a lack of variation in laboratory test requirements between early phase and later phase clinical trials of the same agent. Again, this observation may suggest that these eligibility criteria remain static, not taking into account new or developing knowledge.

Implications of Laboratory Eligibility Criteria

How do laboratory eligibility criteria impact clinical trial enrollment? A recent study examining 10,500 electronic health records of patients with advanced non-small cell lung cancer (NSCLC) found that expanded criteria that would allow patients with advanced NSCLC and brain metastases, previous or concurrent cancers, and limited kidney function to enroll in clinical trials would nearly double the percentage of patients potentially eligible to enroll in clinical trials.¹⁵ This analysis demonstrated that requiring CrCl ≥ 60 mL/min resulted in exclusion of almost 15% of patients. Furthermore, real-world evidence suggests that enrolling patients with renal dysfunction may not necessarily have an adverse impact on study outcomes. In an analysis of more than 12,000 cancer patients with evaluable renal function from the Flatiron Health electronic health record database, baseline renal dysfunction was not associated with any differences in on-treatment outcomes or survival.¹⁶ Given the prevalence of renal dysfunction in some oncology populations (e.g., over 20 percent of individuals with lung cancer), relaxing renal function requirements in the absence of specific contraindications might have major impact on trial enrollment and improve the applicability of trial results.¹⁷ Instances may still exist where strict eligibility criteria are required for patient safety. For example, a drug that causes hemolytic anemia or risk of bleeding may require patients to have a higher hemoglobin criteria for entry; However, a drug without any known effect on this parameter may not require this and could be adequately managed expectantly according to best oncologic care.

Differences Between and Within Drug Classes

Laboratory-based criteria should reflect treatment considerations, including organ function adequate for drug metabolism and elimination, and to provide a sufficient margin in the event of hepatic or renal toxicity of investigational treatments. Therapies that may be hepatically metabolized or renally excreted would be expected to have more narrow enrollment criteria than those which are eliminated via other means.

Among medical therapies, substantial differences in metabolism/excretion and toxicity profiles render broad recommendations challenging. In some instances, multiple drugs in a class would be expected to have comparable profiles, as is the case for PD-1/PD-L1 immune checkpoint inhibitors. Minor pharmacologic differences within the class, such as IgG subtype (IgG1 versus IgG4) or antibody species (human versus humanized), do not translate into meaningful variation in laboratory requirements. By contrast, ALK inhibitors approved for ALK-positive lung cancer differ substantially in pharmacodynamic properties, resulting in truly distinct metabolic and toxicity profiles.¹⁸ With this in mind there will need to be some variability, but data and experience from similar in-class molecules should be used to inform selection of laboratory requirements for eligibility criteria. Furthermore, as investigational therapies advance from early phase to late phase development, those criteria should be adjusted based on earlier experience and observations. The current “cut and paste” approach should be challenged and clinical trial protocols continuously re-evaluated as recommended in FDA guidance.¹⁹

Laboratory Test Value Variability

Importantly, laboratory test values may differ substantially between testing facilities and among populations. For instance, the lower limit of normal for hemoglobin is 9.6 g/dL in Black women, which falls below the eligibility threshold for some clinical trials.²⁰ Additionally, study criteria that use ANC > 1500/ μ L can contribute to significant racial disparities in studies as a result of benign ethnic neutropenia.²¹ Lowering the ANC cutoff level could increase the number of eligible minority patients that may have benign ethnic neutropenia. Across populations, among 38 standard laboratory tests analyzed among more than 3,000 healthy individuals in the National Health and Nutrition Examination Survey (NHANES), only five (glucose, phosphorus, potassium, total bilirubin, and uric acid) did not show significant racial/ethnic difference in distribution.²² For instance, the normal range of serum creatinine for White females was 0.50–1.10 mg/dL, but 0.43–0.88 for Asian females. Furthermore, formulas used to assess CrCl often vary widely.²³ Black participants had significantly higher normal ranges in CPK, globulin, and total protein, and lower normal ranges in hematocrit, hemoglobin, total cholesterol, triglycerides, and WBC than Whites. There are also differences according to gender. For alanine aminotransferase (ALT), upper reference ranges vary from 35 U/L to 79 U/L for men, and 31 U/L to 55 U/L for women.²⁴ Other laboratory tests with significant differences between males and females include total bilirubin, cholesterol, bicarbonate, calcium, and total protein.²² To the best of our knowledge, we cannot identify the rationale for one of the most common liver dysfunction criteria—Transaminases of 2–2.5 x ULN for most patients, and sometimes up to 5x with liver metastases. The number of patients this excludes from studies is unknown but is felt to represent a significant burden especially in patients who may have adequate synthetic and clearance function but have elevated transaminases due to liver metastases. Current FDA guidance suggests that patients with transaminase elevation up to 20x ULN may have similar tolerance to therapies as those with normal levels.^{19,25}

Advanced age also represents a key consideration in laboratory test interpretation, as many patients with common cancers are elderly. Alkaline phosphatase increases by 20% between the 3rd and 8th decade. CrCl increases by 10 mL/min/1.73 m² per decade. Postprandial glucose increases by 30–40 mg/dL per decade after age 40.²⁶ Between the sixth and eighth decades, platelet count decreases by approximately 20,000/mcL.²⁷

Laboratory test results in cancer populations.

Across cancer types, laboratory abnormalities are more common in oncology populations. Anemia, when defined as Hgb <11 g/dL, occurs in up to 40–60% of patients with common malignancies.²⁸ This is especially true in patients who have already received several treatments for their malignancy, and can be supported easily with transfusions or other care. In terms of renal function, 50% patients with cancer have CrCl < 90 mL/min and 20% have CrCl < 60 mL/min.²⁹ For drugs that are known not to be renally metabolized, this may not be relevant, and only reflect the general performance status of the patient. Further, the formulas used to estimate glomerular filtration rate (e.g. Cockcroft Gault) often underestimate true CrCl, especially in females and those that are older with less body mass. More direct measures (e.g., 24 hour urine CrCl) should often be used. Furthermore, the prevalence of laboratory abnormalities is greatest in patients with more advanced cancer,

which tend to represent the cases for which a clinical trial may be most appropriate and potentially most beneficial.^{30,31}

RECOMMENDATIONS

The group concluded that laboratory tests should be used as exclusionary criteria only when clearly necessary due to safety or efficacy concerns. As demonstrated previously, laboratory-based eligibility criteria are frequently carried forward from earlier protocols to new trials, without critical scientific evaluation of the need and impact of these decisions. Because each clinical trial focuses on specific patient populations and studies specific therapies with differing toxicity and pharmacokinetic considerations, it is not feasible to provide specific lab test value thresholds for broad applicability. Nevertheless, the incorporation of the key principles (Table 2) may help ensure safety and optimize efficacy, while minimizing unnecessary patient exclusions.

CONCLUSION

Overall, this working group found that laboratory test-related eligibility criteria (1) may account for exclusion of a meaningful proportion of patients from clinical trials (2) rarely change over time or over the course of a therapeutic agent's clinical development; (3) are highly similar between drug classes that have substantially different pharmacologic and toxicity profiles; and (4) may have varying impact on patients according to age, gender, and race/ethnicity. We have outlined a number of areas in which modifying current clinical trial eligibility and following the principles of distributive justice may optimize trial participation and efficiency, and applicability of study results to better inform appropriate uses of new therapies. Recommendations outlined in this manuscript can help guide appropriate use of laboratory tests and testing intervals as exclusionary criteria in protocols. This would enable increased clinical trial accrual and provide more relevant data that better mirror the oncology patient populations that ultimately will be treated with these agents. While it is reasonable to establish some minimum criteria for safety, they should be appropriately broad without compromising safety. This will allow oncologists to have more evidence-based discussions with patients and caregivers regarding the potential risks and benefits, ultimately improving shared decision-making in cancer care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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STATEMENT OF TRANSLATIONAL RELEVANCE

Stringent eligibility criteria, including laboratory test thresholds, may restrict clinical trial enrollment and limit the relevance of study results. The American Society of Clinical Oncology (ASCO) and Friends of Cancer Research (*Friends*) worked with stakeholders throughout the cancer research community to develop evidence-based, consensus recommendations to modernize the use of clinical trial laboratory test-related eligibility and intervals. These recommendations may help to facilitate accrual and render trial populations more representative of the disease population, improving the generalizability of the research results.

Figure 1. Frequency of laboratory value requirements according to therapy type for 107 oncology clinical trial protocols for solid tumors.

Protocol-specified accepted laboratory test values and number of protocols with each requirement for (A) absolute neutrophil count (ANC), (B) platelet count, (C) hemoglobin, (D) serum creatinine, (E) creatinine clearance or glomerular filtration rate (GFR), (F) total bilirubin, and (G) AST and ALT.

Figure 2. Frequency of laboratory value requirements according to therapy type for 16 oncology clinical trial protocols for hematologic malignancies.

Protocol-specified accepted laboratory test values and number of protocols with each requirement for (A) absolute neutrophil count (ANC), (B) platelet count, (C) hemoglobin, (D) serum creatinine, (E) creatinine clearance or glomerular filtration rate (GFR), (F) total bilirubin, and (G) AST and ALT. NC, no criteria specified.

Table 1.

Oncology Clinical Trial Distribution by Trial Phase and Therapy

Trial Characteristic	# of Solid Cancer Trials (%) (n=107)	# of Hematology-Oncology Trials (%) (n=16)
<i>Trial Phase</i>		
I	71 (66%)	11 (69%)
I/II	19 (18%)	4 (25%)
II	8 (8%)	1 (6%)
III	9 (8%)	0 (0%)
<i>Therapy Category</i>		
Targeted/Small Molecule	37 (35%)	5 (31%)
Immunotherapies	46 (44%)	7 (44%)
Chemotherapy	14 (13%)	1 (6%)
Combination	8 (8%)	3 (19%)

Table 2.

Recommendations for Broadening Laboratory Reference Ranges and Testing Intervals

<p>1. Laboratory tests should only be used as exclusionary criteria when scientifically justified and when abnormal test results confer safety concerns.</p> <p><i>Laboratory test requirements should be customized to the therapy/therapies under investigation.</i> Ultimately, laboratory test requirements should reflect study therapy pharmacokinetics and pharmacodynamics and anticipated toxicities. For instance, if a therapy does not undergo hepatic metabolism and is not expected to cause hepatic toxicity, strict hepatic function eligibility criteria may not be necessary, or at a minimum, there should be very broad entry criteria. Wherever data is available from similar agents, previous experience should be used as a guide. For example, in some instances (e.g., PD1/PDL1 checkpoint inhibitors) pharmacology and toxicity profiles are similar across agents, allowing use of comparable laboratory-related eligibility criteria. In other instances (e.g., ALK inhibitors), each individual drug may have different requirements depending on its individual PK/PD profile. Importantly, restrictions from earlier clinical trials should not be carried forward automatically but should be modified to reflect the experiences of patients in earlier trials and in post-market use.</p> <p><i>Laboratory test-related eligibility criteria should not be used as a surrogate for performance status or the presence of comorbidities.</i> Due to the older age of most cancer patients and the likelihood of identifying laboratory anomalies of no clinical significance, the use of laboratory tests to identify sufficiently healthy individuals is likely to result in unnecessary exclusion of potential patients. Instead, clinical trial protocols should specify functional status and comorbidity requirements in line with previous recommendations, as appropriate.¹⁰</p> <p><i>Consider adjusting laboratory-based eligibility criteria broadly rather than in specific clinical scenarios.</i> A frequent clinical trial practice is to relax laboratory-related eligibility criteria in populations more likely to have baseline laboratory abnormalities (e.g., allowing lower levels of renal function in patients with genitourinary malignancies, or allowing greater degrees of hepatic dysfunction in patients with primary or metastatic liver cancer). If these population subgroups can be treated effectively and safely, consideration should be given to applying similar laboratory-related eligibility criteria more broadly.</p> <p><i>Laboratory-based eligibility criteria should be limited to the clinical concern.</i> As an example, in clinical trials of therapies that may prolong the QTc interval, low levels of electrolytes such as potassium, calcium, and magnesium may increase risk of cardiac arrhythmias. A common response to this concern is to require levels of these electrolytes to be within normal limits. This results in unnecessary exclusion of patients whose electrolyte levels are slightly above the normal range, even though there is no increased risk of QTc prolongation. In these cases, precise protocol writing (e.g., requirements for laboratory tests to be above the lower limit of normal rather than within normal limits) with an understanding of the intent of the criteria and the normal variations among people as outlined above is of utmost importance. Furthermore, opportunities to allow for correction to the near-normal range should be allowed. While safety is of utmost concern, protocols should reflect the intended use population for the treatment being evaluated and not situations where the trial data cannot realistically be applied to post approval scenarios.</p> <p><i>Inter-laboratory variation should be accounted for when selecting laboratory-based eligibility criteria.</i> It is important to consider thresholds rather than specific normal values. ULN's can vary across labs, and criteria should reflect multiples of ULN, rather than absolute numbers (akin to NCI CTCAE criteria). Across academic medical centers, there are substantial differences in serum creatinine determination, with laboratory site accounting for 50% and time of assay performance accounting for another 15% of this variation.³² CrCl should be accounted for by accurate measurements, and options for direct measurements (24-hour urine CrCl) be allowed rather than formulas that simply estimate the clearance (e.g., Cockcroft-Gault).</p>	<p>2. Laboratory reference values should account for potential normal variations due to race, ethnicity, age, sex, and gender identity (i.e., due to surgical and hormonal changes).</p> <p><i>The impact on trial eligibility, enrollment, and relevance should be assessed when selecting laboratory-based eligibility criteria.</i> Laboratory abnormalities occur frequently without clinical significance. Reference intervals generally include 95% of test results obtained from a presumably healthy population. The chance that a healthy person has a test result falling outside this range is 5% for a single test, but rises to 64% for 20 tests (e.g., complete blood count and metabolic panel).³³ As noted previously, the likelihood of test results outside reference ranges is far greater among individuals with cancer and may not be of clinical significance with respect to the treatment being studied.</p> <p><i>Demographic differences in laboratory test results, and their implication across populations, should be understood.</i> Given the differences among ethnicities, those criteria that are included should be sufficiently broad to allow for these natural variations.^{22,34} It should be noted that persons who have undergone surgery or take medications to align with their gender identity may have altered "normal" lab values despite being healthy.^{35,36}</p>	<p>3. Routine re-assessment of laboratory test-based exclusion criteria should be conducted during the course of clinical research and drug development as investigational agents progress from earlier to later phase clinical trials.</p> <p><i>Eligibility criteria should be expanded based on earlier clinical experience and in the absence of safety concerns.</i> Phase 1, first-in-human trials should incorporate strict laboratory-related eligibility criteria as a precautionary measure, as the clinical pharmacology and toxicity profile of the novel therapy are not known. However, once these characteristics have been established, laboratory-related eligibility criteria should be adjusted to reflect this experience enabling appropriate access to therapies under investigation. Currently, the initial criteria are often carried forward to Phase 2 and Phase 3 trials, resulting in unnecessarily strict requirements and exclusion of potential patients, and limiting applicability of results. Similarly, criteria and experience from drugs of a similar class may be used to formulate eligibility entry criteria.</p> <p><i>Broadening eligibility criteria by employing less stringent requirements for laboratory eligibility requirements should be accounted for when assessing on-treatment abnormal laboratory values.</i> In addition to grading of laboratory abnormalities using CTCAE, which accounts for the most severe laboratory value aberration, interpretation of results should take into account CTCAE AE attribution. If patients have baseline laboratory anomalies prior to starting treatment, they may have more frequent and more severe laboratory abnormalities after initiating therapy. To account for this possibility, one approach is to focus on the <i>degree of change</i> in laboratory values, as conveyed by shift tables.³⁷ Shift tables display baseline laboratory values and the shift at post-dose, which helps determine the potential impact of the investigational therapy on these results.</p>
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4. Increasing the intervals between protocol-specific tests should be considered to help reduce patient burden and increase ability to rely on routine clinical testing, especially in later cycles of treatment and over the evolution of protocols from earlier to later phase clinical trials.

Restrictive test intervals could result in reduced interest in and commitment to clinical trials among patients, clinicians, and investigators. Oncology patients, in general, are spending an inordinate amount of time for treatment of their cancer. The average informed consent form for oncology trials is over 4,000 words and describes hundreds of procedures.³⁸ Unnecessary testing and procedures can lead to more patients choosing not to participate in trials or dropping out over the course of a study. Minimizing testing frequency to reflect what is truly needed to assess safety and efficacy may improve interest, enrollment, and adherence on clinical trials.

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