870 additional deaths within 6 months after treatment, at a total cost of $208,800,000 (870 × $240,000).

Accordingly, whether vemurafenib will be a justifiable addition to our financially strained health care system remains uncertain.

Jason P. Lott, M.D.
Yale University School of Medicine
New Haven, CT
jason.lott@gmail.com

No potential conflict of interest relevant to this letter was reported.

1. Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. BMJ 1999;319:1492-5.
2. Maharaj R. Adding cost to NNT: the COPE statistic. ACP J Club 2008;148:A8.
3. Cancer facts and figures 2010. Atlanta, GA: American Cancer Society, 2010. (http://www.cancer.org/Research/CancerFacts Figures/CancerFactsFigures/cancer-facts-and-figures-2010.)
4. Miller AJ, Mihm MC Jr. Melanoma. N Engl J Med 2006;355:51-65.

THE AUTHORS REPLY: Morita and Nagai ask about correlation between the response to vemurafenib and the ratio of BRAF V600E to BRAF wild-type DNA. Tumor DNA was tested with the use of a qualitative polymerase-chain-reaction–based assay that showed the BRAF V600E mutation as being either detected or not detected. We did not determine whether tumors were heterozygous or homozygous for the mutated allele. They also ask about possible mechanisms of resistance to vemurafenib. This open question is still being pursued by many investigators. Data so far indicate that melanomas developing resistance to vemurafenib reactivate the MAPK pathway. Other resistance pathways are possible. We expect that these different resistance mechanisms will soon be clarified and will lead to strategies to avoid or delay resistance.

In five patients with melanoma with the BRAF V600E mutation who received vemurafenib, Dalle et al., using aggressive dermatologic surveillance, observed six atypical lesions, five of which were considered to be BRAF wild-type primary melanomas. Vemurafenib and other compounds that inhibit mutated BRAF can activate BRAF wild-type cells that are driven by elements upstream in the MAPK pathway. We believe this is the likely explanation for the increased incidence of cutaneous keratoacanthomas, warts, and low-grade squamous-cell carcinomas seen with these drugs. The pagetoid scatter and subtle cytologic atypia seen in the figure by Dalle et al. certainly indicate an unusual nevus, but not all pathologists would consider this to be a bona fide melanoma. However, the diagnostic threshold is somewhat subjective. Aside from these five cases, only five other cases of superficial melanoma have been reported among the other 464 patients treated by other investigators in the phase 2 and 3 trials. There have been no cases of aggressive or metastatic secondary cancers as of this writing, although data are lacking concerning this drug. We agree that patients treated with vemurafenib should be monitored closely and that suspicious cutaneous lesions should be excised.

Lott questions the cost-effectiveness of vemurafenib therapy. Because of the short median follow-up at the time of our interim analysis, his calculation cannot consider long-term survival benefits beyond 6 months; this will require longer follow-up. Also, the actual median cost of vemurafenib treatment is approximately half of what Lott indicates in his letter. Still, we agree with his overall point that it is important to take a hard look at how we, as a society, spend our health care dollars.

Paul B. Chapman, M.D.
Memorial Sloan-Kettering Cancer Center
New York, NY
chapmanp@mskcc.org

Axel Hauschild, M.D.
University of Kiel
Kiel, Germany

Grant A. McArthur, M.B., B.S., Ph.D.
Peter MacCallum Cancer Center
Melbourne, VIC, Australia

Since publication of their article, the authors report no further potential conflict of interest.

Antagonistic T-Cell Subsets in Skin Diseases

TO THE EDITOR: Eyerich et al. (July 21 issue)[1] evaluate patients presenting with both psoriasis and atopic eczema, and they conclude, on the basis of their distinct cytokine profiles and reactivity to nickel, that T cells infiltrating these different lesions target different antigens.

However, they did not investigate at the clonal level either the T-cell receptor clonal signa-

tures involved or their formal peptide-antigen specificity.

"Fate-mapping" studies (to determine the cellular derivatives of a cell or population of cells) show that T cells are intrinsically unstable both in vitro and in vivo.[2,3] We recently analyzed both cytokine profiles and T-cell-receptor $\alpha\beta$ sequences at the clonal level,[4] and we found that psoriasis lesions are infiltrated by Th1, Th17, Th22, and Th2 cells. Importantly, T-cell-receptor $\alpha\beta$ sharing was observed across all T-cell subsets. Therefore, T-cell subsets with distinct cytokine profiles may share the same antigen specificity.

We agree with Eyerich et al. that cytokine profiles, reactivity to nickel, and skin colonization may be different between psoriasis lesions and atopic eczema lesions, but this does not formally show that different antigen-specific T-cell subsets determine the pathogenesis of these diseases.

Laurent Arnaud, M.D.
Martin Larsen, Ph.D.
Guy Gorochov, M.D., Ph.D.

Centre Hospitalier Universitaire Pitié–Salpêtrière
Paris, France
guy.gorochov@psl.aphp.fr

No potential conflict of interest relevant to this letter was reported.

1. Eyerich S, Onken AT, Weidinger S, et al. Mutual antagonism of T cells causing psoriasis and atopic eczema. N Engl J Med 2011;365:231-8.
2. Lexberg MH, Taubner A, Albrecht I, et al. IFN-gamma and IL-12 synergize to convert in vivo generated Th17 into Th1/Th17 cells. Eur J Immunol 2010;40:3017-27.
3. Hirota K, Duarte JH, Veldhoen M, et al. Fate mapping of IL-17-producing T cells in inflammatory responses. Nat Immunol 2011;12:255-63.
4. Larsen M, Arnaud L, Hié M, et al. Multiparameter grouping delineates heterogeneous populations of human IL-17 and/or IL-22 T-cell producers that share antigen specificities with other T-cell subsets. Eur J Immunol 2011;41:2596-605.

TO THE EDITOR: We would like to focus on the characteristics of Patient 2 described by Eyerich et al. This patient had high total IgE titers (3944 IU per milliliter), atopic eczema, and skin colonization by *Staphylococcus aureus*. All these findings are observed in the hyper-IgE syndromes.[1] Although heterogeneous, the hyper-IgE syndromes are in many cases characterized by impairment in Th17 development; however, the hyper-IgE syndromes with a milder phenotype and ability to develop Th17 responses have been described recently.[2] Patient 2 could have had a hyper-IgE syndrome; the cumulative data on the production of cytokines and the lack of data on T-cell stimulation with microbial or fungal antigens do not address this issue. High levels of total IgE are often a hallmark of partial T-cell immunodeficiency and immune dysregulation[3]; indeed, we note that all the patients affected by atopic eczema and psoriasis had a total IgE level that was significantly higher than that of patients with psoriasis and allergic contact dermatitis (Table 1 of the article by Eyerich et al.). A further characterization of these patients could improve our understanding of the development of psoriasis and atopic eczema.

Francesco Borriello, M.D.
Raffaele De Palma, M.D., Ph.D.

Second University of Naples
Naples, Italy
raffaele.depalma@unina2.it

No potential conflict of interest relevant to this letter was reported.

1. Schimke LF, Sawalle-Belohradsky J, Roesler J, et al. Diagnostic approach to the hyper-IgE syndromes: immunologic and clinical key findings to differentiate hyper-IgE syndromes from atopic dermatitis. J Allergy Clin Immunol 2010;126(3):611.e1-617.e1. [Erratum, J Allergy Clin Immunol 2010;126:1015.]
2. van de Veerdonk FL, Marijnissen RJ, Joosten LA, et al. Milder clinical hyperimmunoglobulin E syndrome phenotype is associated with partial interleukin-17 deficiency. Clin Exp Immunol 2010;159:57-64. [Erratum, Clin Exp Immunol 2011;164:289.]
3. Liston A, Enders A, Siggs OM. Unravelling the association of partial T-cell immunodeficiency and immune dysregulation. Nat Rev Immunol 2008;8:545-58.

THE AUTHORS REPLY: Arnaud et al. refer to the controversial field of T-cell evolution and plasticity. In our minds, three major questions are unresolved to date. First, does an antigen drive differentiation of distinct T-cell subsets (e.g., pollen, a preferred Th2 differentiation),[1] or are other (intrinsic) factors determining the subset? Second, once differentiated, are T cells stable or do they change their phenotype? Third, even if a T cell potentially secretes distinct cytokines, under what circumstances does it operate in vivo? For all these questions, conflicting evidence exists, and our article gives further hints to the great mosaic. First, as stated by Arnaud et al., all T-cell subsets are present in both psoriasis lesions and atopic eczema lesions, although the proportions differ.[2] However, when stimulated with cognate allergen, atopy patch test–derived T cells produced almost exclusively interleukin-4. This finding argues for the fact that allergen-specific T cells in atopic eczema are predominantly Th2 cells. Furthermore, intrinsic alterations in the skin are not sufficient to elicit psoriasis or atopic eczema, since the two can coexist in one person. Thus, distinct antigens appear to trigger different T-cell responses that subsequently initiate a disease-specific local mi-

croenvironment. However, we agree with Arnaud et al. that the exact molecular basis of T-cell activation, especially in the case of psoriasis, needs to be addressed in further studies.

Borriello and De Palma address the important aspect of clinical decision making. Historically, the diagnosis of atopic eczema and the hyper-IgE syndrome has been based on clinical phenotyping and laboratory findings. Patient 2 did not fulfill these criteria for the hyper-IgE syndrome.[3] However, as Borriello and De Palma state, both diseases are heterogeneous, and the clinical presentations overlap. With increasing knowledge of altered molecular pathways and distinct genetic mutations, several disease subgroups may be identified. Such a process has been observed in the field of cancer, in which detailed knowledge of the pathogenesis of diseases such as melanoma[4] is the basis for an individualized molecular therapy. Interestingly, no patient with atopic eczema in our article was filaggrin-deficient, which could indicate a "T-cell-driven" or "antigen-dependent" type of atopic eczema. Certainly, the way to proceed is to identify the precise molecular and genetic alterations of individuals rather than groups of patients.

Stefanie Eyerich, Ph.D.
Helmholtz Center Munich
Munich, Germany
kilian.eyerich@lrz.tum.de

Anna T. Onken, M.D.
Kilian Eyerich, M.D., Ph.D.
Technische Universität Munich
Munich, Germany

Since publication of their article, the authors report no further potential conflict of interest.

1. Traidl-Hoffmann C, Mariani V, Hochrein H, et al. Pollen-associated phytoprostanes inhibit dendritic cell interleukin-12 production and augment T helper type 2 cell polarization. J Exp Med 2005;201:627-36. [Erratum, J Exp Med 2005;201:1347.]
2. Eyerich S, Eyerich K, Pennino D, et al. Th22 cells represent a distinct human T cell subset involved in epidermal immunity and remodeling. J Clin Invest 2009;119:3573-85.
3. Grimbacher B, Holland SM, Gallin JI, et al. Hyper-IgE syndrome with recurrent infections — an autosomal dominant multisystem disorder. N Engl J Med 1999;340:692-702.
4. Curtin JA, Fridlyand J, Kageshita T, et al. Distinct sets of genetic alterations in melanoma. N Engl J Med 2005;353:2135-47.

Coagulopathy of Chronic Liver Disease

TO THE EDITOR: In their review article, Tripodi and Mannucci (July 14 issue)[1] present data that suggest a procoagulant imbalance in cirrhosis. Resistance to anticoagulation that is mediated by thrombomodulin[2] and an increased relative risk of venous thromboembolism[3] indicate that patients with cirrhosis do not undergo anticoagulation because of their increased prothrombin time. Consequently, the rationale to administer fresh-frozen plasma to correct the prothrombin time before invasive procedures is debated.

One of the invasive procedures that is most frequently performed in patients with decompensated cirrhosis is diagnostic or large-volume paracentesis. Even in patients with elevated values for the international normalized ratio, bleeding after paracentesis occurs in a very low percentage of patients,[4] and there is no evidence that a prolonged prothrombin time is associated with a risk of bleeding after this procedure.[5] These findings indicate that a prolonged prothrombin time is not associated with a clinically relevant hypocoagulable state in patients with cirrhosis. Therefore, avoiding the administration of fresh-frozen plasma before paracentesis in patients with cirrhosis should be considered, since the risks and costs may exceed the real benefit for the patient.

Andrea De Gottardi, M.D., Ph.D.
University of Bern
Bern, Switzerland
andrea.degottardi@gmail.com

No potential conflict of interest relevant to this letter was reported.

1. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Engl J Med 2011;365:147-56.
2. Tripodi A, Primignani M, Chantarangkul V, et al. An imbalance of pro- vs anti-coagulation factors in plasma from patients with cirrhosis. Gastroenterology 2009;137:2105-11.
3. Søgaard KK, Horváth-Puhó E, Grønbaek H, Jepsen P, Vilstrup H, Sørensen HT. Risk of venous thromboembolism in patients with liver disease: a nationwide population-based case-control study. Am J Gastroenterol 2009;104:96-101.
4. Pache I, Bilodeau M. Severe haemorrhage following abdominal paracentesis for ascites in patients with liver disease. Aliment Pharmacol Ther 2005;21:525-9.
5. De Gottardi A, Thévenot T, Spahr L, et al. Risk of complications after abdominal paracentesis in cirrhotic patients: a prospective study. Clin Gastroenterol Hepatol 2009;7:906-9.

TO THE EDITOR: Tripodi and Mannucci indicate that anticoagulation should be commonly used