

# Association of Minimal Residual Disease With Clinical Outcome in Pediatric and Adult Acute Lymphoblastic Leukemia

## A Meta-analysis

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 Supplemental content

**IMPORTANCE** Minimal residual disease (MRD) refers to the presence of disease in cases deemed to be in complete remission by conventional pathologic analysis. Assessing the association of MRD status following induction therapy in patients with acute lymphoblastic leukemia (ALL) with relapse and mortality may improve the efficiency of clinical trials and accelerate drug development.

**OBJECTIVE** To quantify the relationships between event-free survival (EFS) and overall survival (OS) with MRD status in pediatric and adult ALL using publications of clinical trials and other databases.

**DATA SOURCES** Clinical studies in ALL identified via searches of PubMed, MEDLINE, and clinicaltrials.gov.

**STUDY SELECTION** Our search and study screening process adhered to the PRISMA Guidelines. Studies that addressed EFS or OS by MRD status in patients with ALL were included; reviews, abstracts, and studies with fewer than 30 patients or insufficient MRD description were excluded.

**DATA EXTRACTION AND SYNTHESIS** Study sample size, patient age, follow-up time, timing of MRD assessment (post-induction or consolidation), MRD detection method, phenotype/genotype (B cell, T cell, Philadelphia chromosome), and EFS and OS. Searches of PubMed and MEDLINE identified 566 articles. A parallel search on clinicaltrials.gov found 67 closed trials and 62 open trials as of 2014. Merging results of 2 independent searches and applying exclusions gave 39 publications in 3 arms of patient populations (adult, pediatric, and mixed). We performed separate meta-analyses for each of these 3 subpopulations.

**RESULTS** The 39 publications comprised 13 637 patients: 16 adult studies (2076 patients), 20 pediatric (11 249 patients), and 3 mixed (312 patients). (The EFS hazard ratio (HR) for achieving MRD negativity is 0.23 (95% Bayesian credible interval [BCI] 0.18-0.28) for pediatric patients and 0.28 (95% BCI, 0.24-0.33) for adults. The respective HRs in OS are 0.28 (95% BCI, 0.19-0.41) and 0.28 (95% BCI, 0.20-0.39). The effect was similar across all subgroups and covariates.

**CONCLUSIONS AND RELEVANCE** The value of having achieved MRD negativity is substantial in both pediatric and adult patients with ALL. These results are consistent across therapies, methods of and times of MRD assessment, cutoff levels, and disease subtypes. Minimal residual disease status warrants consideration as an early measure of disease response for evaluating new therapies, improving the efficiency of clinical trials, accelerating drug development, and for regulatory approval. A caveat is that an accelerated approval of a particular new drug using an intermediate endpoint, such as MRD, would require confirmation using traditional efficacy endpoints.

JAMA Oncol. doi:10.1001/jamaoncol.2017.0580  
Published online May 11, 2017.

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**M**inimal residual disease (MRD) refers to the presence of disease in cases deemed to be in complete remission by conventional pathologic analysis. Detecting MRD in various hematological malignant diseases has been associated with higher relapse rates. These include chronic myeloid leukemia (CML), acute myeloid leukemia (AML), acute and chronic lymphoblastic leukemia (ALL and CLL), and multiple myeloma.<sup>1-8</sup> In CML, the detection of chimeric BCR-ABL messenger RNA (mRNA) in peripheral blood has become the standard of care for assessing disease response, and has been used as a marker of disease response in registration studies.<sup>1,2</sup>

In individual studies of ALL, the detection of MRD has been associated with poorer event-free survival (EFS) and overall survival (OS). US and European pediatric studies use risk stratification based on postinduction or postconsolidation MRD status, increasing therapy in cases with substantial MRD and/or decreasing therapy in patients who achieve MRD negativity.<sup>9,10</sup>

Using MRD status to stratify risk in adult patients with ALL may play a role similar to that in pediatric patients with ALL.<sup>11-13</sup> For example, a 2-stage risk-adapted study in adults found that 72% of patients who achieved MRD negativity were disease-free after 5 years compared with only 14% of the MRD-positive patients, regardless of clinical risk category.<sup>12</sup>

Using MRD assessment to guide clinical treatment may depend on the strength of association, its robustness across studies, its dependence on disease subtype and the patient's clinical and demographic characteristics. A critical consideration is the extent to which the ability to predict clinical outcome from a patient's MRD status depends on treatment.

Minimal residual disease in patients with ALL can be measured in several ways, including by multiparametric flow cytometry (MFC), by polymerase chain reaction (PCR) of the IgH VDJ and/or TCR gene rearrangements, and by leukemia-specific fusion transcripts (eg, BCR-ABL). Although MRD levels assessed using molecular and immunophenotypic approaches are highly correlated,<sup>14-17</sup> differences in sensitivity and the potential for analytic variability has clouded their interpretation.

Minimal residual disease is a measure of disease burden following a specific therapeutic intervention, and thus of therapeutic response. Minimal residual disease status has a potential impact on clinical management, trial design, and drug development. However, the wide adoption of MRD as a meaningful end point has been limited by the difficult interpretation of the data across heterogeneous studies, treatments, and individual patients. To understand the association of MRD with clinical outcomes EFS and OS, we performed a literature-based meta-analysis of ALL studies, distinguishing by patient age. We addressed the extent to which absence of MRD correlated with better long-term clinical outcome in the context of therapies considered in literature reports.

## Methods

### Data Sources

Two investigators (S.Z. and H.H.) conducted independent searches of PubMed, MEDLINE, and clinicaltrials.gov using

### Key Points

**Question** What role does minimal residual disease (MRD) status have in acute lymphoblastic leukemia (ALL)?

**Findings** We used prospective inclusion criteria to identify 39 studies with 13 637 patients. For both pediatric and adult patients with ALL, MRD negativity was associated with much better long-term outcome. For example, 10-year event-free survival for MRD negativity vs MRD was 77% vs 32% for pediatrics and 64% vs 21% for adults.

**Meaning** In patients with ALL, MRD status is a useful indicator of therapeutic benefit in clinical practice and has potential for making drug development more efficient by providing early evidence of treatment benefit.

various ranges of publication dates and key words, including “MRD,” “ALL,” “minimal residual,” and “acute leukemia.” We surveyed disease experts to augment our candidate list of published studies.

### Study Selection

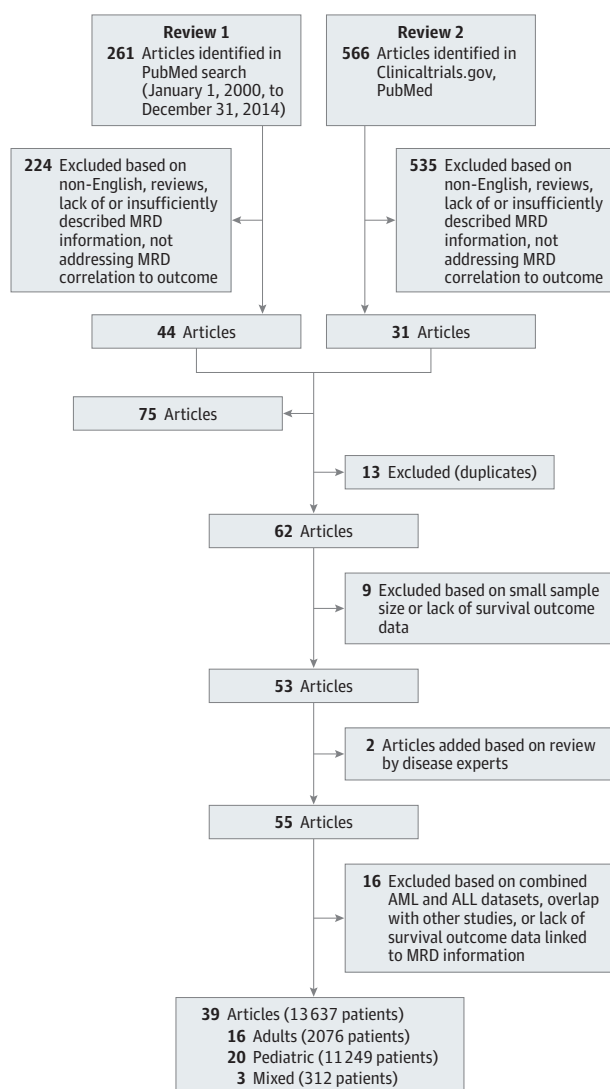
We excluded reviews and abstracts, studies with fewer than 30 patients, studies with insufficient description of MRD assessment, and studies that provided no information regarding survival end points (either EFS or OS) by MRD status. We performed separate analyses for adult, pediatric, and mixed adult/pediatric populations where the last category refers to studies that include at least 20% of both age groups (Figure 1).

### Data Extraction

We extracted from publications the following information when it was available: study sample size, median age and age range, median follow-up time, MRD detection method (PCR vs MFC using at least 3 colors), MRD cutoff level, MRD determination time point(s), ALL phenotype (B cell, T cell), cytogenetics including Philadelphia chromosome positivity (Ph<sup>+</sup>), and survival outcomes. Two researchers (S.Z. and L.M.) extracted the data independently.

We used a sequential approach when extracting hazard ratios (HRs), comparing patients who achieved MRD negativity with those who did not: (1) When available we used observed HRs and their CIs. (2) If Kaplan-Meier (KM) curves for both MRD-negative and MRD-positive groups were provided we used the commercial graph digitizer software DigitizeIt (version 2.1, Bormisoft) to extract coordinates of points on the curves and applied a numerical algorithm to reconstruct survival results.<sup>18</sup> We then calculated HRs and CIs. When sample sizes over time were not available we adjusted the results by estimating the censoring over time based on reported follow-up time distribution and sample sizes. (3) For articles that provided survival proportions at fixed time points (eg, 3 years or 5 years), their standard deviations, and numbers of patients, we estimated the study's HR and its CI assuming that the time-to-event distribution was exponential.<sup>19</sup> We excluded a study if none of these 3 possibilities were available for either EFS or OS.

Figure 1. Literature Search Diagram



### Data Synthesis

Searches of PubMed and MEDLINE found 268 to 566 articles depending on keywords and date range (January 1, 2000 to December 31, 2014, vs no restriction). A parallel search on clinicaltrials.gov using key words “acute lymphocytic leukemia,” “acute lymphoblastic leukemia,” “minimal residual disease,” and “MRD” found 67 closed trials and 62 open trials as of 2014. Publications related to these studies were identified and merged. We excluded reviews, abstracts, nonEnglish language articles, studies with MRD method obsolete or insufficiently described, and those with no survival end points. This left 62 publications with 30 285 patients. Applying additional exclusions of studies with fewer than 30 patients and insufficient outcome follow-up information reduced the total to 39 publications (16 adult, 20 pediatric, and 3 mixed) of distinct studies with 13 637 patients. These studies<sup>5,6,9-13,20-51</sup> formed the basis of our statistical analyses (eTable 1 in the Supplement).

Our search and study screening process adhered to the PRISMA Guidelines.<sup>52</sup> Characteristics of the individual studies are presented in eTable 1 in the Supplement. In all the studies MRD was assessed in bone marrow. Some studies assessed MRD in blood as well.

### Statistical Analyses

The primary end points were EFS and OS. We included disease-free, recurrence-free, relapse-free, and event-free survival in the definition of EFS.

For each study we obtained hazard ratios (MRD-negative vs MRD-positive) and CIs in 1 of the 3 ways described in Data Extraction above. We modeled log-HRs separately for pediatrics, adults, and mixed. We assumed that hazards were constant within each 6-month period of follow-up. We truncated results of all studies at 15 years. Each 6-month segment has its own study-specific hazard rate, and therefore also its own HR of MRD-negative vs MRD-positive.

We used 2 different approaches for statistical analysis, both of which allowed for the possibility that MRD status has different effects in different studies. The primary analysis used a Bayesian hierarchical model.<sup>53-55</sup> The other approach was a traditional frequentist random-effects model.<sup>55,56</sup> For the Bayesian analysis we assumed the prior distribution of the mean log-HR across studies to be normal with mean  $m$  and standard deviation  $s$ . We assumed noninformative prior distributions for  $m$  and  $s$  and for the time-segment-specific baseline hazard rates.

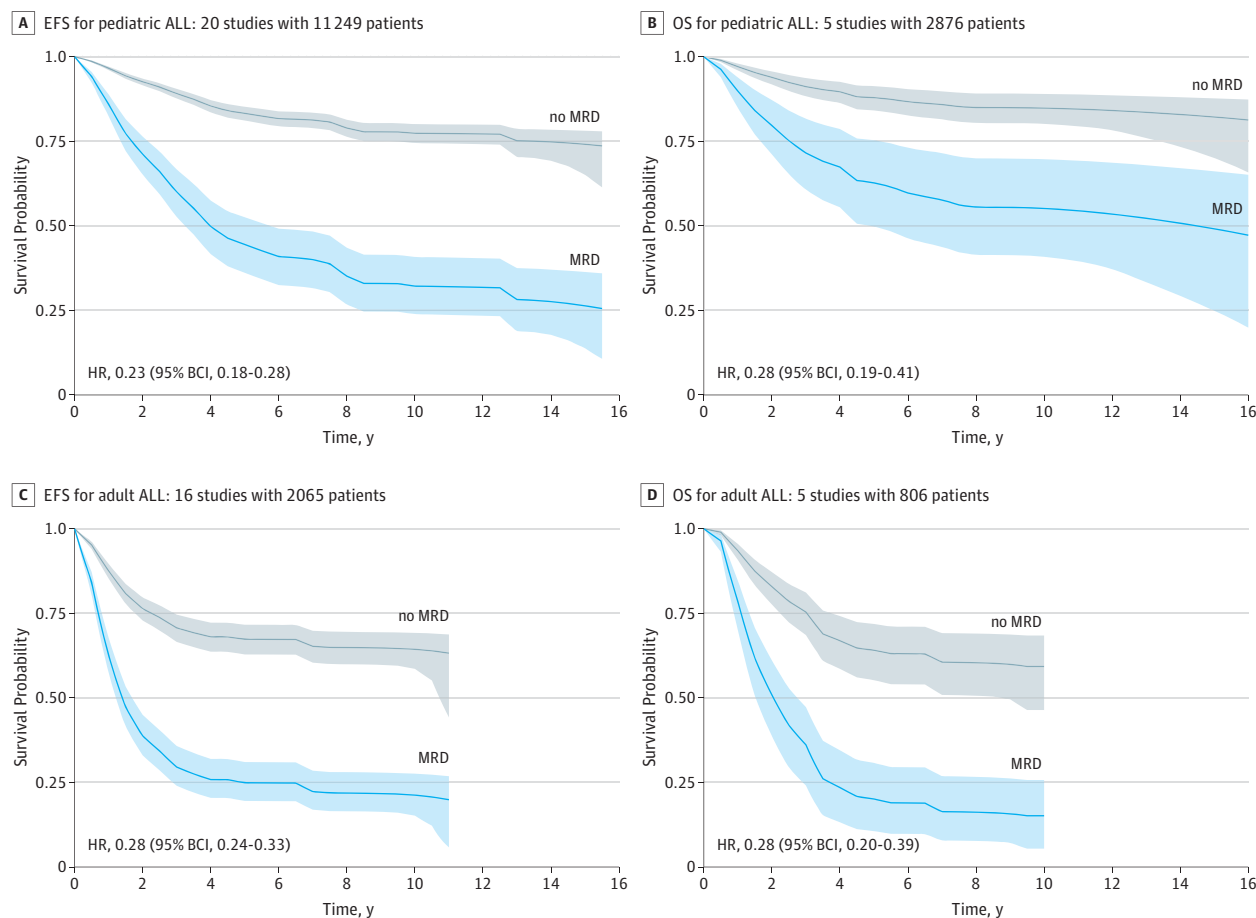
Unless indicated otherwise, all results reported are based on Bayesian hierarchical analysis. In particular, estimated HRs are posterior means and their variability is indicated by 95% Bayesian credible intervals (BCIs).

Studies that reported the observed HRs depending on MRD status and the associated CIs—case 1—contribute directly to the probability distributions of the log-HRs of the studies considered and in particular to inferences about the mean of the studies. For studies that reported KM curves for MRD-positive and MRD-negative groups—case 2—we estimated hazard rates within each time segment by reconstructing the time-to-event data. The contribution of studies that provided survival proportions only at particular time points—case 3—we assumed constant hazards over the time periods that were provided by the publications.

For all Bayesian analyses we found the joint posterior distributions of model parameters using Markov chain Monte Carlo (MCMC) methods. Because closed forms of the “full-conditional distributions” are not available, we generated these distributions using Gibbs sampling and a Metropolis-Hastings computational algorithm.<sup>54</sup> We used statistical software R (version 3.1.2, R project; with packages `survival_v2.38-1`, `rjags_v3-14`, `coda_v0.16-1`, `lattice_v0.20-29`, and `ggplot2_v1.0.1`) and JAGS statistical software (version 3.4.0, <http://mcmc-jags.sourceforge.net>) for data analysis.

For the Bayesian analyses we plotted the means of EFS and OS distributions for patients who achieve MRD negativity vs those who did not. We used shading to show the 95% BCIs about these mean curves. Similarly we present the mean HR for MRD-negative vs MRD-positive and the 95% BCI of the HR.

Figure 2. Estimated Survival Curves for Patient Groups With ALL



A, EFS: 3191 patients at time 0 with MRD and 8058 with no MRD. B, OS: 883 patients at time 0 with MRD and 1993 with no MRD. C, EFS: 711 patients at time 0 with MRD and 1354 with no MRD. D, OS: 242 patients at time 0 with MRD and 564 with no MRD. The plots show the means of the Bayesian hierarchical analyses. The shadings associated with each curve show the 95% BCIs for the mean survival

proportion at the corresponding point in time of follow-up. All 20 pediatric studies and all 16 studies contributed to the EFS distributions (A and C) whereas only 5 of the studies in each age group contained information about OS (B and D). ALL indicates acute lymphoblastic leukemia; BCI, Bayesian credible intervals; EFS, event-free survival; MRD, minimal residual disease; OS, overall survival.

In reporting probability distributions of HRs for subgroups of patients we included only those studies for which relevant published evidence was available. We excluded studies from a subgroup analysis if the publication did not include information regarding survival by MRD status for the subgroup in question. An extreme example that contained little evidence for an important subgroup is Philadelphia chromosome status in pediatric studies. Only 2 pediatric studies restricted eligibility by Ph-status and both studies consider only Ph-negative disease. As a consequence, for pediatric Ph-negative ALL the CI will be relatively wide and for pediatric Ph-positive ALL it does not exist.

This project was approved by the MD Anderson institutional review board.

## Results

### Studies Available for Analysis

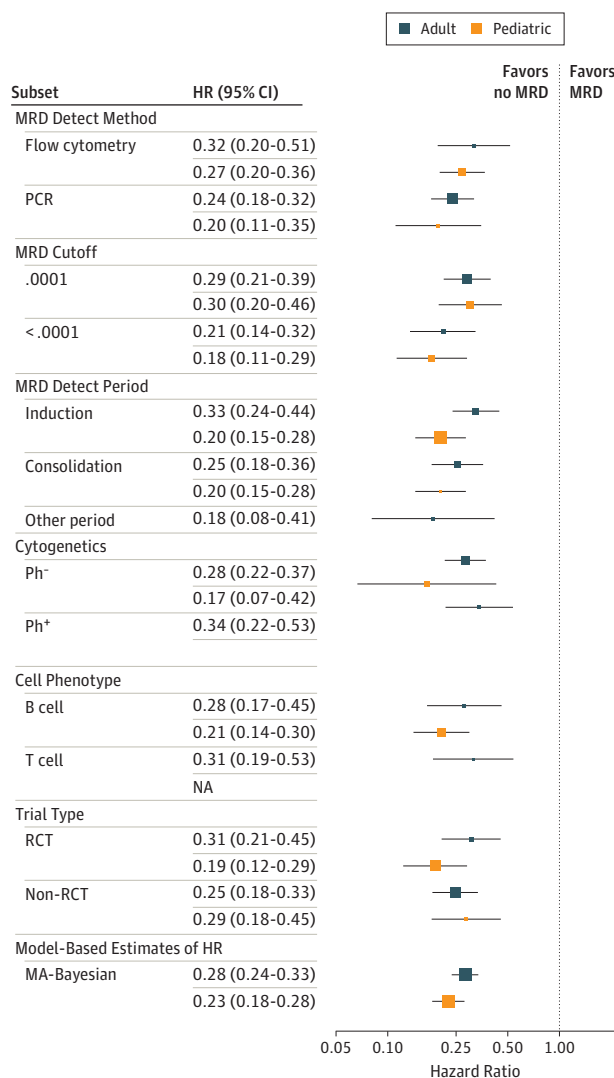
A total of 39 studies (16 adult, 20 pediatric, and 3 mixed) were available for analysis, including 13 637 patients. These stud-

ies are described in eTable 1 in the Supplement. They used MRD status in various ways. Some were compilations of several clinical trials merged into a single study of MRD. For example, Borowitz et al<sup>9</sup> assessed MRD status retrospectively on archival samples from 2143 pediatric patients enrolled in several Children's Oncology Group trials. In another type of study, Vora et al<sup>10</sup> used MRD status prospectively as a randomization criterion. The goal was to address the possibility of delaying and reducing treatment intensity. Patients with undetectable or low MRD (<0.01%) were randomized to 1 or 2 courses of delayed intensification therapy. In a third study type, Bassan et al<sup>12</sup> used MRD status in adults as an indicator of recurrence risk, with MRD-negative patients receiving conventional therapy while those with MRD received high-dose therapy, including allogeneic transplantation.

### MRD and Outcomes

The overall EFS results for pediatric and adult studies are shown in Figure 2, A and C. For pediatric patients, EFS was better for those who achieved MRD negativity—estimated EFS of 77%

Figure 3. Forest Plot of EFS HRs for Pediatric and Adult ALL Subtypes



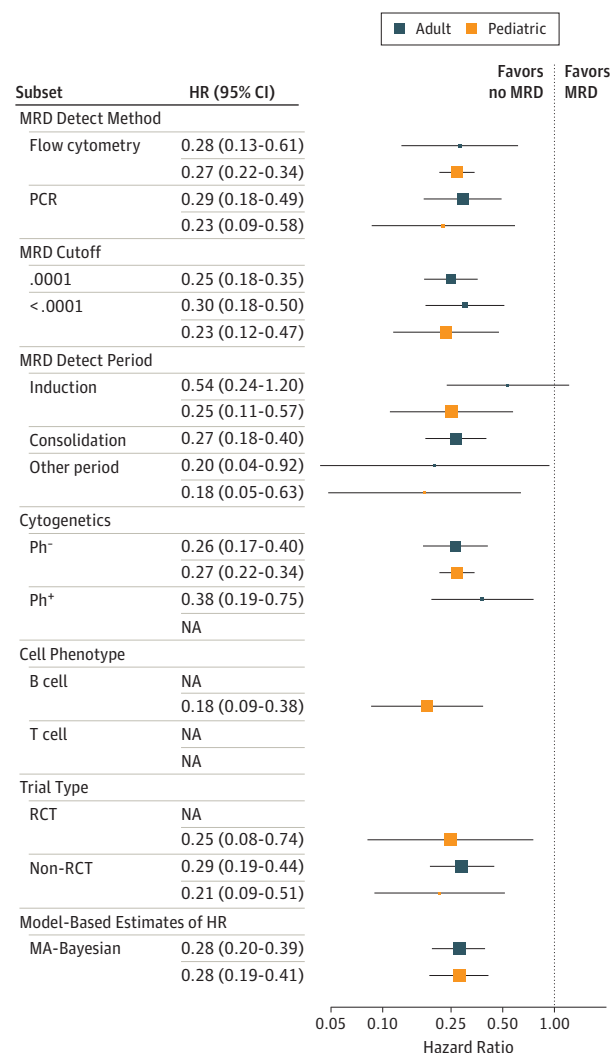
Numerical results are in eTable 2 in the Supplement. The dots represent the mean HR for the Bayesian hierarchical analysis. The horizontal lines show the 95% BCIs for the subgroup's EFS HR. ALL indicates acute lymphoblastic leukemia; EFS, event-free survival; OS, overall survival.

at 10 years—compared with those with positive MRD—approximately 32% at 10 years. Although EFS for adult patients was inferior to that for pediatric patients in respective MRD groups, there was a similarly strong association between MRD and outcome. Adults who were MRD-negative had EFS of approximately 64% at 10 years vs only 21% for those who were MRD-positive. The relative benefit in EFS of having achieved MRD negativity was comparable in both age groups (HR, 0.23; 95% BCI, 0.18-0.28 for pediatric cases and HR, 0.28; 95% BCI, 0.24-0.33 for adults).

Figure 2, B and D show that the estimated benefit in OS of MRD negativity was identical in pediatric patients (HR, 0.28; 95% BCI, 0.19-0.41) and adults (HR, 0.28; 95% BCI, 0.20-0.39).

The HR for each individual study is shown in Figure 3, A and B.

Figure 4. Forest Plot of OS HRs for Pediatric and Adult ALL Subtypes



Numerical results are in eTable 2 in the Supplement. The dots represent the mean HR for the Bayesian hierarchical analysis. The horizontal lines show the 95% BCIs for the subgroup's EFS HR. ALL indicates acute lymphoblastic leukemia; EFS, event-free survival; OS, overall survival.

There were only 3 studies in the mixed-age group. The results in these studies were very similar to those for the other 2 groups.

### Relationships Between MRD Status and Outcome by Subgroup

The HRs of EFS and OS depending on MRD status are shown in Figures 3 and 4; eTable 2 in the Supplement for various subgroups: type of MRD detection (flow cytometry vs PCR), reported “cutoff” value of MRD measurement ( $\leq 0.01\%$  vs  $0.01\%$ -1%), whether MRD determination was made at the end of induction or consolidation, whether including only Ph-negative or Ph-positive patients, B-cell or T-cell phenotype, and whether the study was a randomized clinical trial. None of the subgroupings suggest a differential effect of MRD on the HR of either EFS or OS.



## Discussion

Our meta-analysis demonstrates a consistent and strong association in ALL between MRD and clinical outcomes. The effect is substantial and robust in all subgroups of ALL that we were able to address, both for pediatric and adult patients. In particular, achieving MRD negativity had a consistent and beneficial effect in studies that used different therapies, different assessment methods and cutoff levels, time points, and disease and study subtypes.

Cutoff level showed an unexpected effect (Figure 3; eTable 2 in the Supplement). Namely, a larger cutoff level ( $>0.01\%$  vs  $\leq 0.01\%$ ) shows numerically smaller HRs for EFS, 0.18 vs 0.30 in pediatric ALL and 0.21 vs 0.29 in adult ALL. However, the numbers of studies involved in this comparison and the differences in hazard ratios is small. So this difference may be owing to unknown factors that differ by study and may not imply greater discrimination for the higher cutoff levels.

For the studies we considered, pediatric MRD-negative patients were much more likely to be disease-free after 10 years than those who were MRD-positive, 77% vs 32%, and alive, 84% vs 55%. For adult MRD-negative patients, 64% were disease-free at 10 years vs 21% for MRD-positive, and alive, 60% vs 15%. The HRs for pediatric patients were 0.23 for EFS and 0.28 for OS and for adult patients, 0.28 for both EFS and OS. Although the relative effects are similar, the hazards over time are very different for pediatric vs adult patients. Conditionally on MRD status, hazards are much higher for adult patients than for pediatric patients in the first 3 years. Hazards for adults were comparable or possibly even lower than for pediatric patients in subsequent years. This observation suggests greater heterogeneity in adult ALL, a heterogeneity beyond that which is distinguishable by MRD status.

Our study confirms MRD as a measure of disease burden that is an early response indicator for use in the design and conduct of clinical trials. As such, achieving MRD negativity may qualify as an end point for drug registration.

A precedent is neoadjuvant breast cancer in biomarker-defined subtypes. Accelerated regulatory approval requires showing substantial improvement in the rate of pathological complete response (pCR).<sup>57</sup> The analogy in ALL would be demonstrating a substantial improvement in the rate of MRD negativity.

Minimal residual disease negativity leads to better clinical outcomes in the studies we considered. But this same relationship may not apply for therapies we did not consider. A new therapy might decrease the rate of MRD but not affect clinical outcome. Or it might have no effect on rate of MRD but still improve outcome. Using MRD as a primary end point for accelerated approval of a new drug will require a plan for confirming benefit on EFS or OS.

This issue is important in drug registration trials. For neoadjuvant therapy in breast cancer, achieving a pCR is associated with longer EFS and OS, especially when restricting to particular biomarker subtypes.<sup>19,58</sup> The US Food and Drug Administration guidance describes routes to accelerated approval based on demonstrating substantial improvement in pCR rates.<sup>57</sup> The critical requirement is evidence that improv-

ing pCR rate improves EFS.<sup>57</sup> One route to registration is a single trial demonstrating improvement in both pCR rate (accelerated approval) and EFS (full approval). If applied to ALL, a prospectively randomized trial would have to show improvement in both rate of MRD and EFS.

The results shown in Figure 2 establish a hypothesis regarding the relationship between MRD and EFS regardless of therapy. If the control therapy has a 30% rate of MRD negativity then, under this hypothesis, 30% of the patients will be on the EFS curve for no MRD and 70% will be on the EFS curve for MRD. The resulting control EFS is the respective weighted average of the 2 curves. Make the analogous calculation for experimental therapy with its assumed rate of MRD negativity, perhaps derived from phase 2 trials. Comparing the 2 weighted averages establishes a hypothesis for the HR in a clinical trial with MRD negativity and EFS as coprimary end points.

This approach will likely give a more accurate estimate of EFS HR than traditional approaches. However, there are at least 3 sources of error.<sup>59</sup> One is evident from Figure 2. The curves are estimates with their uncertainty indicated by the shading. This uncertainty should be considered when finding the predictive probability of trial success under the above hypothesis.<sup>19,53</sup> The second source of error is the uncertainty in the assumed rates for MRD negativity for the 2 therapies. These rates in a future clinical trial may differ from historical rates. This source of error can also be incorporated into the predictive probability of trial success.

The third source of error is the most important: the hypothesis provided by Figure 2 may be wrong for 1 or both therapies. In particular, eliminating residual disease may not translate into the same effect on EFS or OS for a new therapy. A solution is using an adaptive phase 3 trial with frequent interim analyses to reestimate the trial's sample size based on accumulating evidence about rate of MRD and its relationship with EFS. The hypothesis presented in Figure 2 can be updated for both therapies.<sup>19,59,60</sup> Such designs will also confirm the association between achieving MRD negativity and reaching a clinical outcome. Sample size reestimation is best carried out based on frequent calculations of the predictive probability of trial success.<sup>61</sup> Such calculations can also be used to stop the trial for futility.

The effects shown in Figure 2 are dramatic, but they may be misleading. Figure 2 compares 100% of the patients vs 0% of the patients who are MRD-negative. No therapy would qualify for such an extreme, especially since control therapy will have some benefit on MRD. Consider the EFS curves in Figure 2, A. The HR of 0.23 is a reflection of the distance between the MRD and no-MRD curves. The hazard of recurrence with MRD is reduced by 77% by achieving MRD negativity. A therapy that improves the rate of MRD negativity by 20 percentage points, say, from 30% for control to 50%, occupies only one-fifth of the distance between these 2 curves. The control arm EFS curve lies 30% of the way from the MRD curve to the no-MRD curve. The experimental arm lies halfway between the 2 curves. The EFS HR implied by Figure 2, A for those 2 derived curves is about 0.80 (calculation not shown). For a clinical trial to show an EFS improvement of this magnitude would require a sample size greater than 1000 patients.

The clear relationship between MRD and EFS that we quantified has applications besides clinical trial design: (1) in clinical practice, assigning patients who have MRD to alternative therapy, perhaps an allograft or a clinical trial; (2) as a research tool for better defining patients at high risk for recurrence and eligibility for clinical trials; (3) assigning highest priority for definitive evaluation in phase 3 trials for therapies that achieve the lowest rates of MRD; (4) providing supportive data in regulatory decisions based primarily on complete response rates with incomplete hematological recovery (as in the approval of blinatumomab<sup>62</sup>); (5) extrapolating from disease types where a therapy has a known effect on other hematological malignant diseases where it shows a benefit on MRD.

### Limitations

There are important caveats when using MRD. Cases in which EFS is long despite having MRD may reflect the genotypic and phenotypic heterogeneity of tumors or their hosts. The MRD-negative cases that relapse early may reflect the limits of assay sensitivity and a very actively growing tumor. Moreover, technical difficulties could give misleading results. Sensitive and specific standardized methods for MRD determination are not widely available outside of specialized centers. Standardization of PCR-based tests has been widely implemented in Europe. Most studies in the United States use flow cytometry for which standardization is more challenging. However, current MRD methods will likely be superseded by next-generation se-

quencing, which appears to be more sensitive than flow cytometry or PCR. Next-generation sequencing may also be easier to standardize.<sup>63,64</sup> In addition, although we supplemented internet searches with surveys of disease experts, the bases of all our analyses are publications. So our study is subject to publication bias. Similarly, it is subject to any biases or errors of the original investigators. Finally, we did not have by-patient data and so could not draw strong conclusions about the roles of MRD in subsets of patients.

Minimal residual disease is a “biomarker” of disease in the powerful sense that MRD *is the disease*. However, no assay is perfect. Although MRD is a direct measure of disease burden and treatment response in ALL, there may be sanctuary sites in the body that contribute to relapse but are not measurable by conventional methods. The next major advance may be a more sensitive and standardized assessment of level of MRD as a continuous measure of disease burden. It would become as standard in clinical care as getting a hematocrit and a white blood count.

### Conclusions

Minimal residual disease status in patients with ALL is an indicator of therapeutic benefit in clinical practice. It has great potential for making drug development more efficient by providing early evidence of treatment benefit. Using MRD status is useful when designing efficient drug registration trials in ALL.

### ARTICLE INFORMATION

**Accepted for Publication:** February 15, 2017.

**Published Online:** May 11, 2017.  
doi:10.1001/jamaoncol.2017.0580

**Author Contributions:** Dr Berry had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Berry and Zhou conducted and are responsible for the data analysis.

**Concept and design:** Berry, Zhou, Reaman, Wood, Jessup, Radich.

**Acquisition, analysis, or interpretation of data:** Berry, Zhou, Higley, Mukundan, Fu, Reaman, Wood, Kelloff, Radich.

**Drafting of the manuscript:** Berry, Zhou, Higley, Mukundan, Fu, Radich.

**Critical revision of the manuscript for important intellectual content:** Berry, Reaman, Wood, Kelloff, Jessup, Radich.

**Statistical analysis:** Berry, Zhou, Fu.

**Obtained funding:** Berry, Jessup.

**Administrative, technical, or material support:** Berry, Higley, Mukundan, Fu, Wood, Kelloff, Jessup.

**Study supervision:** Berry, Higley, Reaman, Jessup, Radich.

**Conflict of Interest Disclosures:** Dr Berry is co-owner of Berry Consultants LLC, a company that designs Bayesian and adaptive clinical trials for pharmaceutical and medical device companies, groups funded by the US National Institutes of Health, and consortia funded by international agencies. No other disclosures are reported.

**Funding/Support:** Scientific and financial support for the FNHI Biomarkers Consortium project, Minimal Residual Disease Detection in Adult Acute

Lymphoblastic Leukemia (MRD in ALL), and this current study are made possible through funding support provided to the FNHI by AbbVie Inc, Amgen Inc, Pfizer Inc, and Genentech Inc.

**Role of the Funder/Sponsor:** These funding organizations had no influence on the design or conduct of the study or the collection, analysis, and interpretation of the results. They reviewed the manuscript and made suggestions for improving the presentation of the results. The funding organizations had no ability to change the manuscript or its conclusions or to influence where or whether the manuscript would be submitted for publication.

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