



**Figure 1. Examples of Lineage-Specific Telomere Lengths in Lymphocytes and Granulocytes as Assessed by Flow Cytometry and Fluorescence In Situ Hybridization.**

Data for four *POT1* mutation carriers are shown relative to the age-adjusted nomogram for each lineage. *POT1* variants are shown above each data point, and the difference from the age-adjusted median telomere length ( $\Delta$ TL) is shown for each carrier. For persons with a clonal mutation detected, the somatically mutant gene and the allele frequency of the largest clone are shown below. The gray data point in Panel A indicates a chronic lymphocytic leukemia (CLL) clone that was detected concurrently with the long telomere population in the lymphocyte gate. The *JAK2* clonal variant encoded p.V617F, and the *DNMT3A* variant encoded p.K693Afs\*19.

discordance between the genetically inferred telomere length (which was determined to be long) and actual measured values (relatively short). We used flow cytometry and fluorescence in situ hybridization (“flowFISH”) to measure telomere length within families and plotted the data relative to healthy controls.<sup>3</sup> The three *POT1* mutation carriers who had a decrease in granulocyte-specific telomere length over a 2-year period had the largest CHIP clones, a finding that supports a model in which clonal evolution accelerates telomere shortening even in the context of germline telomere-maintenance mutations such as in *POT1*. Figure 1 shows examples of relatively short telomere length in granulocytes from persons with germline *POT1* variants, two of whom have acquired a somatic variant in an additional gene that confers susceptibility to clonal hemo-

poiesis (*JAK2* or *DNMT3*). Also shown is the relatively short telomere length of a lymphoid subpopulation from one of the *POT1* mutation carriers, who had chronic lymphocytic leukemia.

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Since publication of the article, the author reports no further potential conflict of interest.

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3. Alder JK, Hanumanthu VS, Strong MA, et al. Diagnostic utility of telomere length testing in a hospital-based setting. *Proc Natl Acad Sci U S A* 2018;115(10):E2358-E2365.

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## Psychosocial Functioning in Transgender Youth after Hormones

**TO THE EDITOR:** Chen et al. (Jan. 19 issue)<sup>1</sup> provide useful data on a cohort of youth who received treatment with cross-sex hormones for gender dysphoria. One finding deserves to be emphasized. Among the 315 participants, 2 died by suicide in 2 years. I calculate an annual suicide

rate of 317 per 100,000 (95% confidence interval, 38 to 1142). This rate is significantly higher than that found among 15,000 adolescents who had been referred to the world’s largest pediatric gender clinic in London, most of whom were not undergoing any endocrinologic intervention. The

annual suicide rate in that cohort was 13 per 100,000.<sup>2</sup> The disparity is significant ( $P < 0.001$  by a two-sample test of proportions).

The relatively high rate of suicide among the participants in the study by Chen et al. is remarkable given that the authors had excluded anyone presenting serious psychiatric symptoms or manifesting suicidal distress. Aside from the two deaths, 11 other participants reported suicidal ideation during a study visit. It is imperative for Chen et al. to report outcomes for their own scale of suicidal ideation, as described in the study protocol (available with their article at NEJM.org), and how these changed over the 2 years.

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

1. Chen D, Berona J, Chan YM, et al. Psychosocial functioning in transgender youth after 2 years of hormones. *N Engl J Med* 2023;388:240-50.

2. Biggs M. Suicide by clinic-referred transgender adolescents in the United Kingdom. *Arch Sex Behav* 2022;51:685-90.

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**TO THE EDITOR:** The recent study by Chen et al. is of substantial observational interest. The obvious weakness, however, is the absence of a randomized control group. Improvements over time could be related to other factors. First, one cannot account for possible regression toward the mean. For example, the scores on the Beck Depression Inventory–II at baseline indicate that two thirds of participants had either minimal or only mild depression. After 24 months, some of the smaller number of participants who had higher baseline scores ended up with scores closer to the baseline mean. Second, one cannot underestimate the nonspecific, beneficial effects of more care and attention. For example, in double-blind, randomized trials of medication interventions, the participants in the placebo group tend to have marked improvement in psychological state over time, an outcome that is generally substantially greater than the small additional changes attributable to the active intervention.<sup>1</sup> Therefore, the results should be interpreted with caution.

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1. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: a clinical review. *Eur Heart J* 2014; 35:1365-72.

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**TO THE EDITOR:** With regard to the editorial accompanying the article by Chen et al., I agree with de Vries and Hannema<sup>1</sup> that rigorous longitudinal outcome studies that provide evidence about whether cross-sex hormones are effective and safe are needed. However, I disagree that Chen et al. provide such evidence. First, multiple prespecified outcomes (e.g., metabolic and physiological measures, substance use, sexual risk behavior, and self-injury)<sup>2</sup> were not reported. A risk–benefit assessment is therefore incomplete. Second, improvements in mental health outcomes were marginal and were observed in female participants only. Moreover, it is impossible to know whether the observed effects were due to concomitant interventions (e.g., psychotherapy or psychotropic medications), regression to the mean, the Hawthorne effect, or multiple other factors. In the related pubertal suppression study, Olson<sup>2</sup> proposed enrolling a comparator group of children who elected not to initiate pubertal suppression owing to “cost, fears given a lack of scientific evidence, etc.” Why was a similar comparator group not proposed for the cross-sex hormone cohort?

Perhaps the most important takeaway from the study by Chen et al. is that cross-sex hormones are not parachutes.<sup>3</sup> Declaring that randomized, controlled trials are unethical for certain medical practices is no longer defensible.<sup>2</sup>

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

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