

Plasmodium vivax tool brief: Point-of-care G6PD diagnostics

This brief aims to provide an overview of point-of-care (POC) glucose-6-phosphate dehydrogenase (G6PD) diagnostics and to point readers in the direction of additional in-depth resources. The content below explains why G6PD testing is necessary, how G6PD status is classified and measured, which diagnostics are commercially available and what studies have been conducted with them, and considerations for successfully adopting G6PD testing. The audiences that may find this brief most useful are national malaria program staff, malaria project implementers, and others seeking a high-level understanding of G6PD diagnostics that could be used in malaria elimination efforts. The information contained within this document was accurate to our knowledge at the time of publication, but please bear in mind that this is a fast-moving field of emerging evidence.

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What is the G6PD enzyme and what does it do?

- The glucose-6-phosphate dehydrogenase (G6PD) enzyme plays a critical role in protecting red blood cells from damage and premature destruction from by-products of normal cell processes as well as oxidative stress that can be caused by some antimalarial drugs.
- Gene mutations occur naturally in humans. On the G6PD gene, some of these mutations disrupt the normal structure and stability of the enzyme, leading to low levels of G6PD activity inside the red blood cells, which is known as G6PD deficiency. Additional information on G6PD deficiency and diagnostics can be found on the vivaxmalaria.org and PATH websites.

Why is G6PD deficiency important for *Plasmodium vivax* patients?

- Although mostly asymptomatic, G6PD deficiency can cause acute hemolytic anemia—triggered by certain infections, fava beans, or some types of drugs. One such drug type is the 8-aminoquinoline drugs such as primaquine and tafenoquine used for the radical cure of *Plasmodium vivax* (*P. vivax*) malaria.
- Primaquine is the only available antimalarial drug currently recommended globally by the World Health Organization (WHO) for the prevention of relapse of *P. vivax*. There is a new single-dose cure called tafenoquine (brand names: Krintafel/Kozenis^a) that was approved by the United States Food and Drug Administration (FDA) and the Australian Therapeutic Goods Administration (TGA) in 2018 and will soon be reviewed by WHO. Tafenoquine, which requires G6PD testing before use, has also been registered in Brazil, Peru, Colombia, and Thailand.
- WHO guidelines state that “the G6PD status of patients should be used to guide administration of primaquine for preventing relapse” of *P. vivax* malaria.¹ WHO recommends G6PD testing before primaquine use as best practice. Details of this [recommendation](#) can be found at the end of this document.
- To prevent drug-induced hemolytic anemia, it is important to identify a patient’s G6PD status before prescribing primaquine or tafenoquine for vivax malaria.^{2–4}

How is G6PD classified?

- To guide patient treatment, G6PD status is classified into three categories: normal, intermediate, and deficient. These classifications reflect the G6PD enzyme levels in a patient’s blood.
- G6PD deficiency is an X-linked genetic disorder. As such, genetically, males can either be G6PD deficient or G6PD normal, whereas females can be G6PD deficient, G6PD intermediate with one normal G6PD allele and one deficient G6PD allele, or G6PD normal.
- The G6PD genetics mean that males tend toward either low G6PD activity levels (G6PD deficient) or higher G6PD activity levels (G6PD normal). In contrast, in females the G6PD activity levels are distributed across a range from deficient, through intermediate, to normal.⁵
- The WHO Technical Specification Series⁶ for in vitro diagnostic medical devices to identify G6PD activity classifies G6PD status of individuals as per the following table.

Table 1. The WHO Technical Specification Series⁶ G6PD status classification.

Male	
G6PD deficient	▪ G6PD activity <30% of the adjusted male median ^b
G6PD normal	▪ G6PD activity >30% of the adjusted male median
Female	
G6PD deficient	▪ G6PD activity <30% of the adjusted male median
G6PD intermediate	▪ G6PD activity 30%–80% of the adjusted male median
G6PD normal	▪ G6PD activity >80% of the adjusted male median

^a Trademarks are owned or licensed to the GSK group of companies.

^b The “adjusted male median” is obtained by first calculating the median male G6PD activity value, then excluding all males with a G6PD activity level equal to or less than 10% of that median, and finally recalculating an “adjusted male median” with the remaining values.⁸

- Krintafel/Kozenis requires an established G6PD activity level of >70% for eligibility for prescription as an antimalarial drug.
- Almost all males and females that are genetically G6PD deficient have G6PD activities below 30%.
- All males that have a G6PD normal gene have G6PD activity levels above 30%, with the majority having G6PD activity levels above 60% to 70%. This is also true for females that are genetically G6PD normal.
- Females with one G6PD normal allele and one G6PD deficient allele can have G6PD activities ranging from below 30% to above 70% but with the majority having intermediate G6PD activities between 30% to 80%.
- These classifications (i.e., normal, intermediate, deficient) defined in percentage terms are universal across countries, yet their specific value (units per gram of hemoglobin) will differ by assay used to measure the activity and possibly also by the population.
- Universal values for G6PD thresholds are likely to be appropriate in defining G6PD deficiency.⁷

How is G6PD measured?





- Several laboratory-based quantitative assays have been used by researchers to determine G6PD status. These include assays manufactured by Trinity Biotech, Randox Laboratories, Pointe Scientific, Sigma-Aldrich, BIOLABO, and Spinreact.⁷ Qualitative tests, such as the fluorescent spot test, have also been commonly used in studies.
- A spectrophotometric assay is considered the “gold standard” for quantitative assessment of enzymatic activity in red blood cells.⁸
- Clinical laboratories that report quantitative test results typically only report G6PD activity in units per gram (U/g) of hemoglobin (Hb) and whether the result is within the laboratory normal range or outside of that range.⁹
- Quantitative diagnostic tests can determine G6PD normal, intermediate, or deficient status.
- To date, qualitative G6PD tests can determine if a sample or patient is above or below the G6PD deficiency threshold of 30% activity but cannot typically identify G6PD intermediate status, which is mainly found in females.
- Fluorescent spot tests are a qualitative G6PD test that have been used for population screening but usually require some basic equipment, electricity, and a functioning cold chain for storage of reagents.¹⁰
- Tafenoquine can be used only with G6PD normal patients and therefore requires the use of quantitative G6PD diagnostics to avoid prescription to G6PD intermediate patients. If tafenoquine is widely used in the future, quantitative diagnostics will be needed to ensure gender equity in access to this single-dose cure.¹¹
- Point-of-care (POC) diagnostics for G6PD deficiency are also now available and have the potential to expand access to safe radical cure and, as such, enable significant progress toward malaria control and elimination goals.

Overview of commercialized POC G6PD tests

Private-sector diagnostics manufacturers and nonprofit organizations like PATH and the Foundation for Innovative New Diagnostics (FIND) have been working to develop and validate POC G6PD diagnostics for several years. Recently, several POC G6PD diagnostics have made it through the development pipeline and have successfully been commercialized. At least one qualitative and three quantitative POC G6PD tests are now on the market. Previously another qualitative G6PD diagnostic in a lateral flow format was commercialized and used in malaria endemic settings, however quality complications have resulted in this

test no longer being marketed. Information on three quantitative and one qualitative POC G6PD tests can be found in Table 2. One of the quantitative G6PD tests below, the FINDER™ G6PD device, has additional diagnostic assay capabilities on the same platform, including reverse transcription-polymerase chain reaction (RT-PCR), immunoassays, and hematology.

Table 2. POC G6PD Tests.

Metric	CareStart™ G6PD Biosensor	STANDARD™ G6PD Analyzer	BinaxNOW™ G6PD Test Device	FINDER™ G6PD
Image				
Manufacturer	WELLS BIO, INC.	SD Biosensor	Abbott	Baebies
Manufacturer in	South Korea	South Korea	United States	United States
Factory gate price (USD)	Refer to manufacturer	Analyzer: 350 Test strip: 3.50	Refer to manufacturer	Refer to manufacturer
Quantitative or qualitative	Quantitative	Quantitative	Qualitative	Quantitative
Operating temperature	10° to 40° C	15° to 40° C	18° to 25° C	19-30° C
Consumable storage temperature	2° to 40° C	2° to 30° C	2° to 30° C	2 to 8° C
Analyzer storage temperature	2° to 40° C	-20° to 50° C	NA	-10 to 35° C
Consumable lifespan	3 months after opening strip vial or 24 months unopened	18 months	24 months	540 days from date of manufacture
Analyzer lifespan	One-year warranty	10,000 uses with a one-year warranty	NA	One-year warranty
Sample type	Capillary, or venous after using a roller mixer for 20 minutes	Venous or capillary	Venous	Venous or capillary
Ability to identify females with intermediate G6PDd	Yes	Yes	No	Yes

Normalizes for hemoglobin level?	No	Yes	No	Yes
G6PD measurement unit (range)	U/dL (0-300)	U/g Hb (0-20)	NA / Color change	U/g Hb (0.8 – 19.7)
Consumables count per box	25	25	25	96
Controls available	Yes	Yes	No	Yes
Time to result	4 minutes	2 minutes	5 minutes (heparin samples) 7 minutes (EDTA samples)	15 minutes
SRA and WHO regulatory approvals	CE mark	WHO ERP on diagnostics risk category 2; CE mark; Australia TGA; submitted to WHO PQ	CE Mark, US FDA 510K approved.	CE Mark, US FDA 510k under review

Abbreviations: CE, European conformity (Conformité Européenne); ERP, Expert Review Panel; G6PD, glucose-6-phosphate dehydrogenase; Hb, hemoglobin; PQ, prequalification; SRA, stringent regulatory authority; TGA, Therapeutic Goods Administration; WHO, World Health Organization.

* The factory gate prices, also known as an ex-works price, will be less than the final cost seen by purchasers because the factory gate price does not include shipping, taxes, distributor markups, and other ancillary costs.

** G6PD activity values are typically measured in U/g Hb (International Units per gram of hemoglobin). When G6PD activity is only reported in U/dL (International Units per deciliter) a separate instrument will be needed to measure hemoglobin and then calculate to U/g Hb. Normalizing for hemoglobin is necessary to understand how much of the G6PD enzyme is present in a given volume of blood. For example, if G6PD enzyme levels are high for a given volume of blood with low Hb or red blood cell count, then that sample could be falsely G6PD normal if not normalized by Hb.

Researchers have published several studies that analyze the performance of these diagnostics in clinical settings, as shown in the table below.

Table 3. Studies analyzing the performance of G6PD diagnostics.

G6PD diagnostic	Evaluation title and key results
CareStart™ G6PD Biosensor	<p>Pengboon P, Thamwarokun A, Changsri K, Kaset C, Chomean S. Evaluation of quantitative biosensor for glucose-6-phosphate dehydrogenase activity detection. <i>PLoS One</i>. 2019;14(12):e0226927. doi: 10.1371/journal.pone.0226927.</p> <ul style="list-style-type: none"> ▪ “[The] diagnostic ability for identifying G-6-PD deficiency had 78% sensitivity, 89% specificity, 56% positive predictive value (PPV), 96% negative predictive value (NPV) and 88% accuracy when stratified by gender.” <p>Weppelmann TA, von Fricken ME, Wilfong TD, Aguenza E, Philippe TT, Okech BA. Field trial of the CareStart Biosensor analyzer for the determination of glucose-6-phosphate dehydrogenase activity in Haiti. <i>American Journal of Tropical Medicine and Hygiene</i>. 2017;97(4):1262–1270. doi: 10.4269/ajtmh.16-0714.</p> <ul style="list-style-type: none"> ▪ “Compared with the spectrophotometric assay, the sensitivity and specificity to determine participants with <60% residual activity were 53.7% and 94.6%, respectively; for participants with 30% residual activity, the sensitivity and specificity were 5.9% and 99.7%, respectively. The biosensor overestimated the activity in deficient individuals and underestimated it in participants with normal G6PD activity, indicating the potential for a systematic measurement error.” <p>Ley B, Alam MS, O’Donnell JJ, et al. A comparison of three quantitative methods to estimate G6PD activity in the Chittagong Hill tracts, Bangladesh. <i>PLoS One</i>. 2017;12(1):e0169930. doi: 10.1371/journal.pone.0169930.</p> <ul style="list-style-type: none"> ▪ “The Biosensor [identified] 19.1% (17/89) of individuals with G6PD activity <30% by spectrophotometry. Sensitivity and specificity for detecting G6PD activity <30% was... .19 (95%CI: 0.12–0.29) and 0.99 (95%CI: 0.98–0.99) respectively for the Biosensor.”
STANDARD™ G6PD Analyzer	<p>Alam MS, Kibria MG, Jahan N, et al. Field evaluation of quantitative point of care diagnostics to measure glucose-6-phosphate dehydrogenase activity. <i>PLoS One</i>. 2018;13(11):e0206331. doi: 10.1371/journal.pone.0206331.</p> <ul style="list-style-type: none"> ▪ “In comparison to spectrophotometry... at 30% cut off [the STANDARD test] had a sensitivity of 100% (95%CI: 88–100) and specificity of 97% (95%CI: 91–99) ... [the] sensitivity and specificity at 70% cut off activity [was] 89% (95%CI: 77–96) and 93% (95%CI: 83–98) respectively for [the STANDARD test].”

	<p>Gerth-Guyette E, Adissu W, Brito M, et al. Usability of a point-of-care diagnostic to identify glucose-6-phosphate dehydrogenase deficiency: a multi-country assessment of test label comprehension and results interpretation. <i>Malaria Journal</i>. 2021;20(1):307. doi: 10.1186/s12936-021-03803-1</p> <ul style="list-style-type: none"> “Seventy-eight percent of all participants in the study (35/45) obtained passing scores on the assessment with minimal training. Responses to the multiple-choice questions indicate that most participants understood well the test intended use, safety claims, and warnings. The greatest source of error regarding the test was around the correct operating temperature. Most test results were also read and interpreted correctly, with the haemoglobin measurement being a more problematic output to interpret than the G6PD measurement.” <p>Pal S, Bansil P, Bancone G, et al. Evaluation of a novel quantitative test for glucose-6-phosphate dehydrogenase deficiency: bringing quantitative testing for glucose-6-phosphate dehydrogenase deficiency closer to the patient. <i>American Journal of Tropical Medicine and Hygiene</i>. 2019;100(1):213–221. doi: 10.4269/ajtmh.18-0612.</p> <ul style="list-style-type: none"> “The STANDARD test performed equivalently to a reference assay for its ability to diagnose G6PD deficiency (< 30% normal) with a sensitivity of 100% (0.95 confidence interval [CI]: 95.7–100) and specificity of 97% (0.95 CI: 94.5–98.5), and could reliably identify females with less than 70% normal G6PD activity with a sensitivity of 95.5% (0.95 CI: 89.7–98.5) and specificity of 97% (0.95 CI: 94.5–98.6).” <p>Zobrist S, Brito M, Garbin E, et al. Evaluation of a point-of-care diagnostic to identify glucose-6-phosphate dehydrogenase deficiency in Brazil. <i>PLoS Neglected Tropical Diseases</i>. 2021;15(8):e0009649. doi: 10.1371/journal.pntd.0009649.</p> <ul style="list-style-type: none"> “In comparison to spectrophotometry, the STANDARD G6PD Test performed equivalently in determining G6PD status in venous and capillary specimens under varied operating temperatures.” “Using the manufacturer-recommended reference value thresholds, the test’s sensitivity at the <30% threshold on both specimen types was 100% (95% confidence interval [CI] venous 93.6%–100.0%; capillary 93.8%–100.0%). Specificity was 98.6% on venous specimens (95% CI 97.9%–99.1%) and 97.8% on capillary (95% CI 97.0%–98.5%).” “At the 70% threshold, the test’s sensitivity was 96.9% on venous specimens (95% CI 83.8%–99.9%) and 94.3% on capillary (95% CI 80.8%–99.3%). Specificity was 96.5% (95% CI 95.0%–97.6%) and 92.3% (95% CI 90.3%–94.0%) on venous and capillary specimens, respectively.”
BinaxNOW™ G6PD Test Device	<p>Osorio L, Carter N, Arthur P, et al. Performance of BinaxNOW G6PD deficiency point-of-care diagnostic in <i>P. vivax</i>-infected subjects. <i>American Journal of Tropical Medicine and Hygiene</i>. 2015 Jan;92(1):22-27. doi: 10.4269/ajtmh.14-0298. Epub 2014 Nov 10. PMID: 25385861; PMCID: PMC4347383.</p> <ul style="list-style-type: none"> “The performance of the BinaxNOW G6PD test compared with the quantitative spectrophotometric analysis of G6PD activity was assessed in 356 Plasmodium vivax-infected subjects in Brazil, Peru, Thailand, and India. In the quantitative assay, the median G6PD activity was 8.81 U/g

	<p>hemoglobin (range = 0.05–20.19), with 11 (3%) subjects identified as deficient. “</p> <ul style="list-style-type: none"> “Sensitivity of the BinaxNOW G6PD to detect deficient subjects was 54.5% (6 of 11), and specificity was 100% (345 of 345). Room temperatures inadvertently falling outside the range required to perform the rapid test (18–25°C) together with subtlety of color change and insufficient training could partially explain the low sensitivity found.” <p>LaRue N, Kahn M, Murray M, et al. Comparison of quantitative and qualitative tests for glucose-6-phosphate dehydrogenase deficiency. <i>American Journal of Tropical Medicine and Hygiene</i>. 2014 Oct;91(4):854-861. doi: 10.4269/ajtmh.14-0194. Epub 2014 Jul 28. PMID: 25071003; PMCID: PMC4183416.</p> <ul style="list-style-type: none"> “Blood specimens were evaluated on the lateral-flow colorimetric test platform BinaxNOW G6PD Test (catalog number 780-000; Alere Inc., Waltham, MA), which must be performed between 18°C and 25°C.” 201 samples were analyzed on both the BinaxNOW G6PD test and the Trinity Biotech quantitative G6PD test which served as the reference assay. “The BinaxNOW assay had 100% sensitivity and 100% NPV for the 10%, 20%, and 30% activity cutoff values, but sensitivity dropped to 82.6% when the cutoff level was 60% of normal, and NPV fell to 97.8%” The BinaxNOW assay had 93.3%, 98.4%, 99.5% and 100% specificity for the 10%, 20%, 30% and 60% cutoff levels, respectively.
	<p>Tinley KE, Loughlin AM, Jepson A, Barnett ED. Evaluation of a rapid qualitative enzyme chromatographic test for glucose-6-phosphate dehydrogenase deficiency. <i>American Journal of Tropical Medicine and Hygiene</i>. 2010 Feb;82(2):210-4. doi: 10.4269/ajtmh.2010.09-0416. PMID: 20133993; PMCID: PMC2813158.</p> <ul style="list-style-type: none"> “The purpose of this study was to compare a new, rapid, qualitative enzyme chromatographic test [BinaxNOW] for deficiency of G6PD to a standard reference method. Samples from 196 G6PD-normal persons and 50 G6PD-deficient persons were evaluated.” “The sensitivity of the experimental rapid test was 0.98 and the specificity was 0.98 using specimens preserved in heparin, and 0.98 and 0.97, respectively, for specimens preserved in EDTA.”
<p>FINDER™ G6PD</p>	<p>Wong RJ, Montiel C, Kunda M, Stevenson DK, Bhutani VK. A novel point-of-care device for measuring glucose-6-phosphate dehydrogenase enzyme deficiency. <i>Seminars in Perinatology</i>. 2020. 0146-00050. doi: 10.1016/j.semperi.2020.151356.</p> <ul style="list-style-type: none"> “40 whole blood samples collected from adults with a mean age of 46.4 ± 14.3 yrs (ranging from 20 to 72) were run on both the FINDER and at [the Pointe Scientific G6PD Reagent Set].” The correlation coefficient (r) between the FINDER™ G6PD results and reference was reported as 0.95.

- *“A Bland-Altman plot showed that the bias of the [FINDER™ G6PD results] method was only +0.67 U/g Hb and standard deviation of the difference was 1.55 U/g Hb of n = 40 subjects.”*

Aside from these commercialized products, researchers and companies are continuing to develop new POC G6PD diagnostics and improve existing ones. Several other qualitative and quantitative POC G6PD diagnostics are under development, and researchers are continuing to evaluate these tests.

Lessons learned from the PAVE project

The Partnership for Vivax Elimination (PAVE) project has been supporting country plans for the adoption of POC G6PD tests since 2019. In several countries where PAVE is supporting the introduction of the tests, the introduction is either imminent, has started in limited areas, or has scaled up nationwide to endemic areas. Countries in the Mekong region are making especially rapid progress in introducing G6PD testing, and the lessons below are largely drawn from these countries. More detailed information on the initial G6PD test introduction in Cambodia and Lao People’s Democratic Republic (PDR) can be found at the [P. vivax information hub](#) website.

Lesson 1: Quality training is essential

Although studies and real-world implementation have shown health care workers can use POC G6PD tests correctly, these diagnostics are still new to most malaria programs and health workers, and they are more complex than malaria rapid diagnostic tests. These two facts make it essential to focus on quality training when adopting G6PD tests. Training that includes practical experience using the G6PD diagnostic followed by a proficiency assessment can help measure trainee comprehension and readiness to use the diagnostic in real-world settings. Practical training and proficiency assessments require close observation of trainees by the trainers; to ensure this close observation, a relatively low trainee-to-trainer ratio and sufficient time allotted to the training is necessary. The PAVE project finds that a trainee-to-trainer ratio of 4 to 1 or perhaps 5 to 1 and a day dedicated to training for new users can help ensure training has the intended results and patients receive quality care.

Lesson 2: Supervision after introduction helps maintain quality

After health care providers have been trained and G6PD diagnostics begin to be used in health facilities, it becomes important to maintain high-quality patient care. This can be particularly challenging in areas where G6PD diagnostics are new or in areas where they are used infrequently due to declining malaria caseloads. To maintain the proper use of G6PD diagnostics in the face of these challenges, G6PD testing oversight should be integrated into ongoing supervision activities. This may require creating new checklists to use during supervision visits, conducting proficiency assessments with some health care providers, and taking the time to retrain health care providers who perform poorly on those assessments. If there are particular concerns around the introduction of G6PD testing, then additional G6PD-specific supervision visits can be programmed, drawing on proficiency assessment scores from the original G6PD test training, and reviewing surveillance data for abnormalities.

Lesson 3: Costs can be reduced by strategic deployment and procurement decisions

G6PD diagnostic costs are usually only a small percentage of overall malaria elimination efforts, nonetheless time should be devoted to reducing costs where possible while avoiding negative impacts on patient access. To reduce the number of G6PD diagnostics procured, national malaria programs have analyzed maps of recent malaria epidemiology and only deployed tests to health facilities that reach a specified caseload threshold. However, patients presenting outside of catchment areas that have G6PD diagnostics will need to be referred to health facilities with G6PD tests, so referral costs and loss to referral will need to be considered as well. Product spoilage can be avoided by checking expiry dates before procurement, requesting a certain percentage of remaining shelf life upon arrival at customs, or by potentially staggering delivery dates to procure some batches with expiry dates further into the future. Costs can also be reduced by procuring G6PD tests via multilateral procurement channels (e.g., United Nations Office for Project Services) that avoid price markups from private sector distributors.

Lesson 4: Use of tried and tested resources can ease the introduction of G6PD diagnostics

PAVE project members have many years of experience helping to develop and validate G6PD tests and supporting G6PD studies across *P. vivax*-endemic countries. Through this experience, PAVE has developed many resources to aid research partners and national malaria programs to adopt and use G6PD diagnostics. One such resource is the G6PD Operational Research Community of Practice (GORCoP), which has published training materials, quality assurance materials, and a series of webinars that can be found at the [GORCoP](#) website. A wider set of resources on *P. vivax*, G6PD testing, and radical cure can also be found within the *P. vivax* Information Hub at vivaxmalaria.org and at the Asia Pacific Malaria Elimination Network's [Vivax Working Group](#) website.

World Health Organization recommendation:¹

- The G6PD status of patients should be used to guide administration of primaquine for preventing relapse.
- To prevent relapse, treat *P. vivax* or *P. ovale* malaria children and adults (except pregnant women, infants aged < 6 months, women breastfeeding infants aged < 6 months, women breastfeeding older infants unless they are known not to be G6PD deficient and people with G6PD deficiency) with a 14-day course of primaquine at 0.25–0.5 mg base/kg body weight daily in all transmission settings.
- In people with G6PD deficiency, consider preventing relapse by giving primaquine at 0.75 mg base/kg body weight once a week for 8 weeks, with close medical supervision for potential primaquine-induced hemolysis.
- When a patient's G6PD status is unknown and G6PD testing is not available, a decision to prescribe primaquine must be based on an assessment of the risks and benefits of adding primaquine.
- For women who are pregnant or breastfeeding, consider weekly chemoprophylaxis with chloroquine until delivery and breastfeeding are completed; then, on the basis of the woman's G6PD status, treat with primaquine to prevent future relapse.

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