# Sensitive diagnostic tools and targeted drug administration strategies are needed to eliminate schistosomiasis

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**Although preventive chemotherapy has been instrumental in reducing schistosomiasis incidence worldwide, serious challenges remain. These problems include the omission of certain groups from campaigns of mass drug administration, the existence of persistent disease hotspots, and the risk of recrudescent infections. Central to these challenges is the fact that the diagnostic tools currently used to establish the burden of infection are not sensitive enough, especially in low-endemic settings, which results in underestimation of the true prevalence of active *Schistosoma* spp infections. This central issue necessitates that the current schistosomiasis control strategies recommended by WHO are re-evaluated and, possibly, adapted. More targeted interventions and novel approaches have been used to estimate the prevalence of schistosomiasis, such as establishing infection burden by use of precision mapping, which provides high resolution spatial information that delineates variations in prevalence within a defined geographical area. Such information is instrumental in guiding targeted intervention campaigns. However, the need for highly accurate diagnostic tools in such strategies is a crucial factor that is often neglected. The availability of highly sensitive diagnostic tests also opens up the possibility of applying strategies of sample pooling to reduce the cost of control programmes. To interrupt the transmission of, and eventually eliminate, schistosomiasis, better local targeting of preventive chemotherapy, in combination with highly sensitive diagnostic tools, is crucial.**

## Introduction

Despite years of sustained control efforts, the global burden of schistosomiasis remains high. An estimated 221 million people worldwide require chemotherapy to prevent schistosomiasis, of whom 90% reside in sub-Saharan Africa.[1] This immense burden is exacerbated by the fact that schistosomiasis is strongly linked to poverty, limited access to potable water, and a paucity of adequate sanitation.[2] Since 2001, WHO has strongly advocated for the control of schistosomiasis morbidity through preventive chemotherapy[3] and, in 2012, urged countries to expand schistosomiasis control programmes towards the elimination of schistosomiasis as a public health problem.[4]

Although there have been successes in reducing the intensity of infections and the morbidity associated with infections through sustained mass drug administration (MDA) campaigns, schistosomiasis remains highly prevalent.[5] In regions that have successfully reduced the intensity of infection, the diagnostic tools that are currently prescribed are no longer reliable for control programmes. These diagnostic methods are not sensitive enough to accurately detect low intensity infections and thereby underestimate the prevalence of active *Schistosoma* spp infections.[6,7] To stop transmission and sustain the elimination of schistosomiasis, changes to the current global strategies to control schistosomiasis are urgently needed.[8,9] The availability of more sensitive diagnostic tools presents an opportunity to revisit these strategies in regions where an interruption of transmission might be feasible.

Strategic changes to advance the global control of schistosomiasis were discussed at an international workshop hosted by Leiden University Medical Center in the Netherlands in September, 2017. The workshop brought together representatives from national control programmes, industry, funders, and academia (research scientists, clinicians, and mathematical modellers) to develop a vision for the sustained, local interruption of transmission and the eventual successful elimination of schistosomiasis.

## Challenges related to the current approach

WHO's current strategy for controlling schistosomiasis focuses on reducing disease morbidity and transmission through periodic, targeted MDA with praziquantel (40 mg/kg of bodyweight) administered to populations at risk of infection.[1] As part of this strategy, the mean prevalence of schistosomiasis is measured in an implementation unit: a geographical area where an MDA programme is being rolled out. This implementation unit can be a whole district or a subdistrict, such as an administrative, health, or education district, and varies in size from country to country (figure A).[10]

### Key messages

- Preventive chemotherapy has been key in reducing the burden of schistosomiasis, but serious challenges remain
- Current diagnostic tools used by control programmes to detect *Schistosoma* spp infections are not sensitive enough
- Re-evaluation and adaptation of the current strategies to control schistosomiasis recommended by WHO is urgently needed
- The use of highly sensitive diagnostic tools is key in breaking the transmission cycle and moving towards sustained elimination of schistosomiasis

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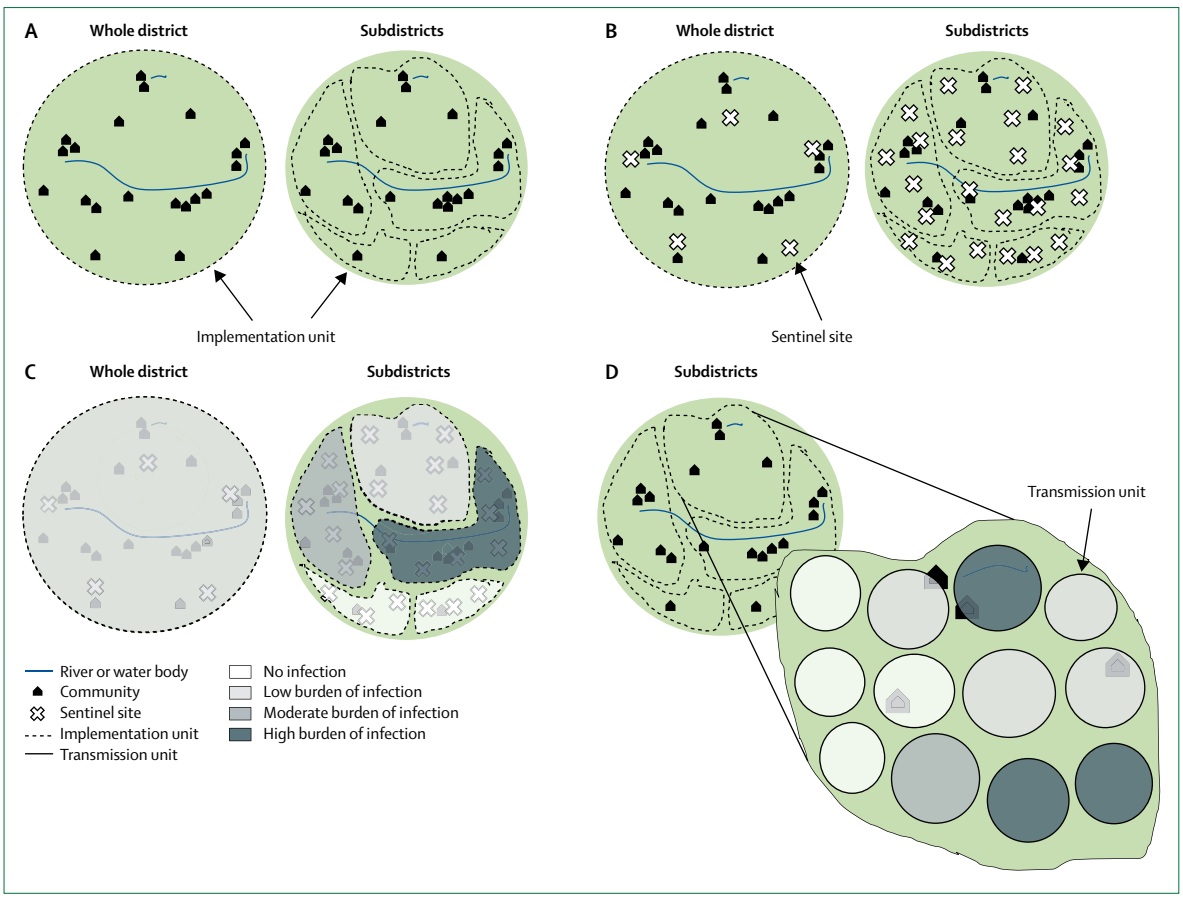


***Figure:*** **Schematic representation of the current strategy of sampling within an implementation unit and the proposed mapping strategy of pooled sampling within subdistricts or transmission units**
(A) According to WHO, areas are divided into implementation units, which can vary in size (eg, a whole district or a subdistrict). (B) The burden of infection in each implementation unit is measured and monitored by sampling from five to ten sentinel sites by use of conventional parasitological diagnostic tools. (C) The burden of infection within an implementation unit is then categorised as low, moderate, or high. (D) By further dividing subdistrict implementation units into smaller transmission units, and, instead of sampling from five to ten sentinel sites, applying a pooling strategy to the whole transmission unit, a bigger area will be sampled from. This strategy results in more accurate data to map and quantify the distribution of schistosomiasis and to identify communities at risk.

Usually, in five to ten sentinel sites within such an implementation unit, a parasitological survey is done to measure the overall prevalence of schistosomiasis in the entire unit (figure B).[9,11] Sentinel sites can be places like schools, with 50 children per school being surveyed. On the basis of the mean prevalence measured by the survey, the burden of schistosomiasis is categorised as low (<10%), moderate (10–49%), or high (≥50%) for the whole implementation unit (figure C), a classification that defines the intervention strategy applied within this geographical area.[12] Even though the burden of infection can be measured in more detail at a subdistrict level, this strategy does not sufficiently capture the focality of schistosomiasis, which results in areas either receiving over-treatment, or, more importantly, under-treatment.[11]

Although initial implementation of WHO's MDA strategy has been successful in reducing morbidity from schistosomiasis,[13–15] there are several opportunities to optimise this strategy. MDA strategies traditionally target school-age children (aged 5–15 years), a group within which the prevalence of schistosomiasis is often high and that can be conveniently reached by programmes at one location (a school). However, this strategy does not protect other groups that are also at a high risk of *Schistosoma* spp infection, including preschool-age children (aged 1–4 years) and adults exposed to infested water through their occupations (eg, fishers, farmers, people who do laundry, and irrigation workers).[1,16] As such, these groups remain potential active reservoirs for continued transmission of schistosomiasis in the community. Children aged 1–4 years are excluded from MDA programmes because of safety concerns and poor adherence to praziquantel. However, the development of a paediatric formulation for praziquantel in 2022 is probable and so this concern is likely to be addressed.[17] Likewise, WHO guidelines recommend the inclusion of pregnant and lactating women in MDA campaigns, but these groups are often excluded because of safety concerns, despite the growing body of evidence that shows the efficacy and safety of praziquantel for treatment of these women.[18,19]

For more on a **paediatric formulation for praziquantel** see https://www.pediatricpraziquantelconsortium.org/

Exclusion of certain groups in MDA programmes becomes a crucial issue when the goal of these campaigns is community-wide control and elimination of schistosomiasis.

The commitment of Merck to support WHO, through the donation of praziquantel for preventive chemotherapy in children aged 5–15 years in sub-Saharan Africa, has been pivotal to schistosomiasis control efforts.[20] However, because of the scale-up of MDA programmes, many African countries have been challenged to equate the demand for praziquantel and the availability of praziquantel in the donation scheme.[21] Moreover, the currently recommended MDA dosage for praziquantel might be leading to suboptimal cure rates and prolonged low intensity infections within some communities. These consequences will be even more substantial and pronounced when the proportion of population coverage by MDA programmes is reduced, leaving large numbers of infected people untreated.

Additionally, in certain areas, control of schistosomiasis is hampered by the existence of persistent hotspots: geographical regions where MDA programmes have been in operation for several years, yet have not engendered the forecasted declines in the prevalence, or intensity, of schistosomiasis.[22–25] Persistent hotspots have been identified across Africa, including ones in Kenya,[26] Mali,[27,28] Sudan,[29] and Tanzania.[22,30] Management of schistosomiasis in these hotspots probably requires integrated control approaches that combine MDA with multisectoral efforts, such as health education, improvements to sanitation and potable water supply, environmental and vector control, and the future use of vaccines.[31–35]

Another challenge in the control of schistosomiasis exists in parts of Asia where the prevalent schistosome species (ie, *Schistosoma japonicum, Schistosoma mekongi,* and *Schistosoma malayensis*) are known to be zoonotic and have several animal definitive hosts as reservoirs of infection.[36] Animal reservoirs for schistosome species have also been described in Africa.[37,38] In such areas, the control and elimination of schistosomiasis is even more difficult because the management of animal reservoirs is imperative.[36] In addition, molecular studies in Africa have also found evidence of genetic interactions between schistosomes in humans and schistosomes in animals and the emergence of hybrid species, indicative of some zoonotic spillover.[39,40]

Diagnosis of schistosomiasis in control programmes is often still based on parasitological assessments of urine or stool samples, depending on the schistosome species endemic in the area. These diagnostic methods are not sensitive enough to detect infections of low intensity and result in an underestimation of infection burden.[7] Identifying areas with low infection intensities by implementing accurate diagnostic tools combined with cost-effective treatment strategies is essential for the elimination of schistosomiasis. This identification is also important for dealing with the so-called subtle morbidities of schistosomiasis, including its effect on cognitive development, which could have long-term effects on the quality of life of individuals.[41] Control programmes are not as effective in low prevalence settings where the factors sustaining low-level transmission are poorly understood and transmission has not yet been interrupted.[9,31,32] In addition, low-endemic areas probably require continuous surveillance with highly sensitive diagnostic tools because the risk of stopping MDA prematurely might cause infection levels to return to those present before MDA (recrudescent infections).[35,42] As for persistent hotspots, an integrated control approach is probably required to achieve these epidemiological targets in these areas.

## The importance of precision mapping and more targeted interventions

Locating exactly where active transmission occurs and identifying which individuals within a community still harbour living adult worms is particularly relevant because schistosomiasis is heterogeneously distributed, which means that an endemic region can be considered as a collection of microfoci.[43] There are no clear guidelines that account for the potential effects of this natural heterogeneity, or focality, on programme design. Studies by the Schistosomiasis Consortium for Operational Research and Evaluation (known as SCORE) have shown a large variability in MDA efficacy at the community level.[22,26] Therefore, existing control guidelines need to be adapted to extend focus to geographical areas of low endemicity in which transmission is likely to be interrupted. In these areas, sampling grids can be narrowed by increasing the number of sites being sampled, a concept that has been termed precision mapping.[11] Using the precision mapping approach in Cameroon, Tchuem Tchuenté and colleagues[11] exhaustively sampled all schools in two schistosomiasis endemic districts representing geographical areas with low and high transmission. This approach produced high-resolution mapping information that showed considerable variations in schistosomiasis prevalence between districts and subdistricts (implementation units), which would not have been detected with the conventional mapping approaches included in current global control strategies. Analysis of data from precision mapping can be used to guide targeted and intensified interventions in high-risk areas, making treatment with donated praziquantel cost-efficient and judicious. Furthermore, this approach presents an opportunity to identify both areas of considerable disease transmission within implementation units and individuals living in low-endemic communities who harbour high intensities of living adult worms (the so-called super-spreaders).[44]

## The importance of highly sensitive diagnostics

The success of any strategy to tackle schistosomiasis hinges on the ability to obtain an accurate measure of infection burden in a given community, as rationalised

by Lord Kelvin in 1883: "when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind".[45] The necessity of accurate diagnostic tools with high sensitivity in these strategies is often neglected. To achieve the goal of schistosomiasis elimination, highly sensitive and highly specific diagnostic tools, which ideally are field-applicable, are needed to monitor the burden of infection.

Several diagnostic tools, such as the widely used and field-applicable point-of-care circulating cathodic antigen test (POC-CCA), have been shown to be useful alternatives to conventional diagnostic methods currently used by national control programmes.[46,47] Although the POC-CCA test has been recommended as a replacement for traditional microscopy,[48] it is limited to the detection of intestinal schistosomiasis and is not sensitive enough to detect infections of low intensity.[49,50] A more promising alternative is the highly sensitive and highly specific laboratory-based up-converting phosphor lateral flow (UCP-LF) test that detects *Schistosoma* spp circulating anodic antigen (CAA).[51–54] The UCP-LF CAA test is a genus-specific test that detects all *Schistosoma* species in blood and urine samples, and might potentially be able to detect a single worm pair by increasing sample volume.[54,55] Furthermore, the UCP-LF CAA test is amenable to testing strategies that use pooled samples.[56] Individuals whose pooled urine samples are found negative by the UCP-LF CAA test can be assumed to be free of schistosome worms or have a quantity below a set threshold of worm load. In CAA-positive urine pools, one or more individuals harbour a worm burden that might be relevant for further transmission. Individual urine samples can then be subsequently tested to identify infected individuals within a positive sample pool, which allows clinicians to only treat infected individuals and thereby save drugs. Compared with more exhaustive sampling approaches, such pooling strategies can potentially reduce the costs of schistosomiasis control programmes.[57] Although the UCP-LF CAA test is still lab-based, steps are underway to develop a version of this test that can be used in the field.[53,56,58] Clearly, a reliable, easy-to-use, and rapid diagnostic test is a prerequisite for the development of test-and-treat strategies, with or without pooled sampling, the facilitation of clinical diagnosis of schistosomiasis in point-of-care settings, and the targeted use of praziquantel.

Other more sensitive and specific diagnostic methods include PCR for the detection of schistosome-specific DNA in clinical samples (ie, urine, stool, or blood).[7,59] One approach that has been designed for field use is loop-mediated isothermal amplification, an advanced DNA-based detection method that amplifies DNA without a thermocycler and, in some instances, can have a sensitivity higher than conventional PCR.[60–62] Isothermal recombinase polymerase amplification for the detection of DNA specific to schistosomes is a technique that is potentially applicable for field use in the identification of *Schistosoma haematobium*[63] and *Schistosoma mansoni*.[64]

## Integrating sensitive diagnostics into an intensified, focal test-and-treat strategy

In a theoretical, schistosomiasis-endemic area comprised of one or more implementation units where the prevalence of infection is low as measured by standard parasitological methods (ie, an overall prevalence <10% and a prevalence of heavy infections <1%), an intensified, focal test-and-treat strategy, which uses highly accurate diagnostic tools, should be implemented to interrupt transmission. When applying the precision mapping approach in such an area, the burden of infection within an implementation unit should be estimated from a larger number of sentinel sites than the five to ten sampling sites conventionally recommended. To save costs when sampling from a larger number of sentinel sites, multiple samples can be pooled to reduce the total number of tests needed.[56,57] Given the focal nature of schistosomiasis, sampling designs should also consider proximity to water contact points (ie, the source of infection) where transmission is suspected.

An implementation unit at subdistrict level can be divided into separate transmission units: a proposed geographical area limited to one or few transmission sites (figure D). So, instead of the current strategy in which five to ten sentinel sites within an implementation unit are being sampled, the whole implementation unit is divided into smaller transmission units. By integrating a pooling strategy that uses a highly sensitive diagnostic test, a whole transmission unit will be sampled and tested, leading to a quantitative evaluation of the overall infection burden within each transmission unit. Mathematical modelling could provide valuable information on the best pooling strategy by taking into consideration age groups or risk groups and expected infection levels (estimated by precontrol endemicity and control histories) to determine optimal pool size.[56,57] Information from existing databases on the correlation between different diagnostic tests could also be used to develop a predictive model to estimate, for example, CAA or DNA loads, and to link these individual measurements to transmission potential within a given area. The outcome of testing pooled samples with a highly sensitive diagnostic test, in combination with the predictions of models, would then guide the prevalence thresholds that should be set to establish the appropriate control strategy for each transmission unit.

From the aforementioned strategy, we envisage four scenarios that might reflect the burden of infection from surveying each transmission unit (panel). The corresponding recommended strategy should then also be implemented at the level of the transmission unit. In transmission units found to have a high infection burden (eg, potential hotspots or persistent hotspots), intense MDA of yearly, or twice-yearly, treatment should be rolled out, following existing control strategies. Additional samples should be taken from children aged 5–15 years and from other groups at high risk of infection (such as fishers, farmers, people who do laundry, and irrigation

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workers) and testing should be stratified according to these groups. The strategy could be adapted to treat each positive group in addition to all children aged 5–15 years and the entire group could be monitored and followed up over a 2 year period. For transmission units in which a moderate infection burden is established, a regular MDA programme of yearly community-wide treatment should be implemented. In areas where the burden of infection is found to be low, an intensified test-and-treat strategy, with multiple rounds of testing and treating per year, should be implemented after the identification of groups at high risk of infection within each community. In addition, this strategy should include the identification, treatment, and monitoring of individuals who still harbour high worm numbers, despite multiple rounds of community-wide treatment. Furthermore, knowledge about local transmission sites, with respect to aquatic biology and social behavioural patterns, is indispensable in reducing exposure to schistosomes. Individual worm burdens (eg, in the case of super-spreaders) could also be included within programmes to guide local or regional interventions. In transmission units found to be negative for schistosomiasis, MDA would not be done, but groups should be followed up and tested over a given period of time by use of a cost-efficient sample pooling strategy. Knowing whether these areas have always been negative or are now negative after prolonged control programmes is important, and is best reflected by the precontrol endemicity, because the monitoring approach depends on the potential for transmission in the area. Obviously, all strategies also need to integrate other multisectoral approaches, such as health education, snail control, and water, sanitation, and hygiene initiatives. Classic xenomonitoring, augmented with DNA methods that can identify infected snail hosts, is especially important to accurately establish environmental risk and monitor schistosome infection in locations where zoonotic spillover might occur.[65] Further innovations, such as the analysis of environmental DNA in water for schistosome signatures with taxon-specific probes, could be very powerful to verify putative interruptions of transmission.[66]

At the national level, a surveillance response mechanism would need to monitor these focal test-and-treat strategies. This mechanism includes predictive modelling to guide the intervention, monitoring of infections, and mechanisms to evaluate interventions.[67] Global positioning system (known as GPS) mapping could be used to identify the precise locations of infected people and their households.[68] However, privacy issues need to be taken into consideration. Certain innovations, such as surveying snail environmental DNA in bodies of water, can be used to monitor transmission.[66,69] Lessons can also be learnt from the Global Polio Eradication Initiative, which monitors poliovirus by use of the environmental surveillance of sewage.[70]

After transmission is presumed to be interrupted, communities should still, ideally, be monitored longitudinally by use of highly sensitive and highly specific assays (ie, the UCP-LF CAA test and, eventually, antibody detection assays). After several years without the detection of new infections, newborn babies and young children should be assessed for their exposure to schistosomes,[42,71] which can be done through targeted testing of antischistosomal antibodies.[72,73] In addition, the movement of individuals from regions that are still endemic for schistosomiasis into post-transmission areas should be monitored, and infected individuals promptly treated.[74] The development of commercially available, highly sensitive tests would be indispensable in targeting these groups in this post-transmission phase.

Given that current programmes to control schistosomiasis in sub-Saharan Africa rely heavily on donated praziquantel for MDA campaigns, the proposed test-and-treat strategy will enhance cost-efficiency. The availability of a paediatric praziquantel formulation for young children will further support and strengthen a community-wide approach towards targeted treatment.

The successful implementation and efficient roll-out of the proposed strategy would hinge on close cooperation between key international players (such as WHO) and stakeholders within endemic countries. Within these countries, engagement with national and local authorities would guarantee local ownership and responsibility for the strategy and its implementation. Targeted implementation at more local levels, such as within a transmission unit, could be more complex because of logistical challenges and the paucity of adequate health-care system structures. Therefore, strengthening overall neglected tropical disease coordination at national and subnational levels, including the building of local capacity, would assure the proper execution of the proposed strategy and effective long-term monitoring, evaluation, and overall strategic sustainability.

Additionally, endemic countries must adopt and incorporate the strategy into the development of their master plans for neglected tropical disease. Incorporation would

***Panel*: Recommended treatment strategy based on infection burden established by pooled sampling**

- High infection burden: intense mass drug administration (annual or biannual treatment of all groups at high risk of infection and community-wide treatment)
- Moderate infection burden: regular mass drug administration (annual community-wide treatment)
- Low infection burden (near elimination): intensified, focal test-and-treat strategy (multiple rounds per year) and frequent surveillance by use of the most sensitive diagnostic tool available in combination with pooled sampling
- No infection burden (anymore): no mass drug administration, but regular surveillance by use of the most sensitive diagnostic tool available in combination with pooled sampling

be achieved through having local and international stakeholders work closely with expert committees from endemic countries, which are responsible for coordinating the direction of national goals and policies for neglected tropical disease (including for schistosomiasis), and ensuring that these policies are in line with regional and global targets. Combining all these efforts to improve the focal implementation of preventive chemotherapy with highly sensitive diagnostic tools is essential to interrupt transmission of, and eventually eliminate, schistosomiasis.

## Conclusion

The persistent and global burden of schistosomiasis despite continuous large-scale MDA requires us to rethink and revise intervention strategies and the diagnostic tools that enable these strategies. Non-invasive testing of pooled samples with highly accurate diagnostic tools should be used by national control programmes in adapted control strategies that ensure cost-efficiency in monitoring and evaluation and as longer term surveillance, especially in areas of low infection intensity. We believe that this proposed strategy will interrupt the transmission of, and eventually eliminate, schistosomiasis.

### Contributors

ASA, GJvD, and PTH led the writing of this Personal View. All authors contributed to the writing, critical revision, and the discussions of the scope of this Personal View, and approved the final manuscript.

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